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Preparation and evaluation of immediate release tablets of piracetam using super disintegrants

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ABSTRACT

The objective of the present study was to develop immediate release tablets of Piracetam in order to achieve rapid release in GIT which might result in enhanced absorption and thereby improved bioavailability. Nine batches of immediate release of Piracetam were prepared by using different ratios superdisintegrants. Drug–excipients interaction was carried out for pure drug and optimized formulations by using FTIR studies. Piracetam tablets were formulated employing different superdisintegrants fusion by direct compression method. All the batches of immediate release tablets were evaluated pre-compression and post-compression parameters. Based evaluation of different parameters it was concluded that formulation of immediate release tablets of Piracetam was successfully done and F6 shows 99.39 % at 45 min.

Keywords: Piracetam, Poloxamer 188, Croscarmellose sodium and Sodium-starch glycolate, immediate release.

INTRODUCTION

Oral route is the most convenient and extensively used for drug administration. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance suitable for industrial production, improved stability and bioavailability. The concept of immediate release tablets emerged from the desire to provide patient with more conventional means of taking their medication when emergency treatment is required. Recently, immediate release tablets have gained prominence of being new drug delivery systems. The oral route of administration has so far received the maximum attention with respect to research on physiological and drug constraints as well as design and testing of product, Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Most immediate release tablets are intended to disintegrate in the stomach, where the pH is acidic. Several orally disintegrating tablet (ODT) technologies based on direct compression. In pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation is at least 70% (preferably 80%) of active ingredient within 4 hours, such as within 3 hours, preferably 2 hours, more preferably within 1.5 hours, and especially within an hour (such as within 30 minutes) of administration. In Formulation of immediate release the commonly Superdisintegrants used are Croscarmellose, sodium, Sodium Starch glycolate and Crospovidone.[1]

Oral route of administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems does not need sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. There is requirement for new oral drug delivery system because of poor patient acceptance for invasive methods, requirement for investigation of new market for drugs and combined with high cost of disease management. Developing new drug

delivery techniques and that utilizing in product development is critical for pharma companies to survive this century.[2,3,4]
The term 'immediate release' pharmaceutical formulation is the formulation in which the rate of release of drug and/or the absorption of drug from the formulation, is neither appreciably, nor intentionally, retarded by galenic manipulations. Immediate release dosage form is those which break down quickly and get dissolved to release the medicaments. In the present case, immediate release may be provided of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not delay, to an appreciable extent, the rate of drug release and/or absorption.[5,6,7]
Immediate release drug delivery is suitable for drugs having long biological half-life, high bioavailability, lower clearance and lower elimination half-life. But main requirement for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat undesirable imperfection or disease.[8]

MATERIALS AND METHODS

Piracetam Provided by SURA LABS, Dilsukhnagar, Hyderabad.Poloxamer 188 from Merck Specialities Pvt Ltd. Croscarmellose sodium from Merck Specialities Pvt Ltd. Sodium-starch glycolate from Merck Specialities Pvt Ltd. Mannitol from Merck Specialities Pvt Ltd. MCC from Merck Specialities Pvt Ltd. Magnesium stearate from Merck Specialities Pvt Ltd. Talc from Merck Specialities Pvt Ltd. Sodium lauryl sulfate from Merck Specialities Pvt Ltd.

Formulation Development

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 dissolved 1000ml of distilled water and mixed.
Preparation of pH 6.8 Phosphate buffer: Accurately measured 250ml of 0.2M potassium Dihydrogen orthophosphate 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 Piracetam

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 206 nm. Hence all further investigation was carried out at the same wavelength.

b) Preparation of Standard graph in pH 6.8 phosphate buffer

100 mg of Piracetam was dissolved in 100ml of Phosphate buffer of pH 6.8., form 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 206 nm by using a UV spectrophotometer.

Table 1: Formulation of Immediate Release tablets

INGREDIENTS	FORMULATION CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Piracetam	400	400	400	400	400	400	400	400	400
Poloxamer 188	50	100	150	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	50	100	150	-	-	-
Sodium-starch glycolate	-	-	-	-	-	-	50	100	150
Mannitol	25	25	25	25	25	25	25	25	25
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate	8	8	8	8	8	8	8	8	8
Talc	10	10	10	10	10	10	10	10	10
Sodium lauryl sulfate %	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Total Weight of Tablet (mg)	700	700	700	700	700	700	700	700	700

Total weight of tablets = 700 mg

Post compression parameters

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

b) Weight variation: Twenty tablets randomly selected from each batch and individually. Weighed the average weight and standard deviation 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.

$$\text{Friability} = ([w_0\text{-}w] / w_0) \times 100$$

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 206 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 Piracetam tablets: Drug release from Piracetam 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 37^0C and at speed of 50 rpm.

5 ml aliquots of dissolution media were withdrawn each time at suitable time intervals (5, 10, 15, 20, 25, 30 and 45minutes) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by UV Spectrophotometer. The concentration was calculated using standard calibration curve.

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.

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 206nm.

Calibration curve of Piracetam: The standard curve of Piracetam was obtained and good correlation was obtained with R^2 value of 0.999, the medium selected was pH 6.8 phosphates Buffer.

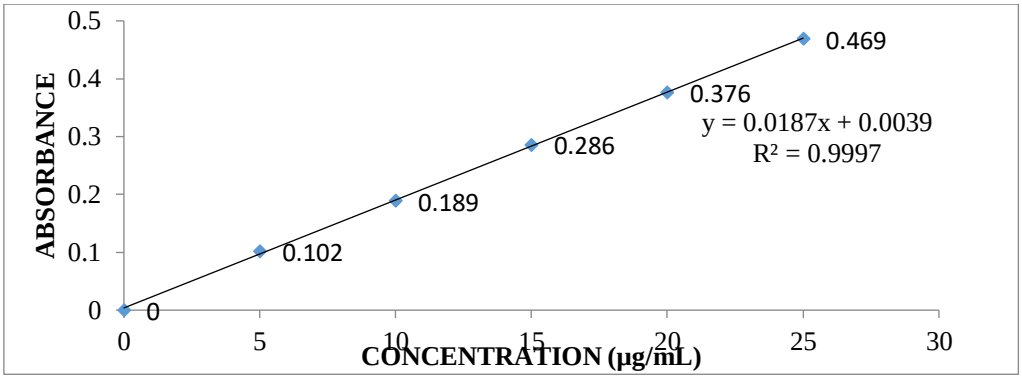

Fig 1: Standard curve of Piracetam

Characterization of precompression blend

Table 2: Physical properties of precompression blend

Formulation code	Angle of repose (Ɵ)	Bulk density (gm/cm^3)	Tapped density(gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	30.86±0.03	0.518±0.25	0.613±0.02	15.35±0.3	1.18±0.01
F2	33.54±0.04	0.522±0.25	0.615±0.04	15.64±0.26	1.175±0.02
F3	30.48±0.02	0.515±1.47	0.610±0.01	15.57±1.4	1.18±0.01
F4	36.27±0.06	0.522±0.34	0.621±0.04	14.87±0.35	1.185±0.06
F5	33.28±0.01	0.517±1.05	0.617±0.03	33.28±0.01	1.185±0.15
F6	34.65±0.08	0.526±0.65	0.614±0.01	15.62±0.72	1.187±0.13
F7	32.19±0.02	0.525±0.99	0.611±0.01	14.91±0.33	1.175±0.03

F8	31.10±0.02	0.522±0.36	0.623±0.02	14.56±0.20	1.170±0.01
F9	39.23±0.01	0.527±0.45	0.618±0.01	16.53±1.6	1.198±0.21

All the values represent n=3

The precompression blend of Piracetam was characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 28.0º, Carr's index values were less than 26 for the precompression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.18 for all batches indicating good flow properties.

Evaluation of tablets

Physical evaluation of Piracetam immediate release tablets

The results of the weight variation, hardness, thickness, friability and drug content of tablets are given in table 10.3. 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 3.1-4.2 kg/cm^2 and the friability values were < than 0.64 % indicating that the tablets were compact and hard. The thickness of the tablets ranged from 5.22 – 5.98 Piracetam. All the formulations satisfied the content of the drug as they contained 95.10 - 99.21 % of Piracetam and good uniformity in drug content was observed. Thus all physical attributes of the prepared tablets were found to be practically within control limits.

Table 3: Physical evaluation of Piracetam

Formulation code	Weight variation (mg)	Thickness (cm)	Hardness (Kg/cm^2)	Friability (%)	Content Uniformity (%)	Disintegration Time (Sec)
F1	698.14	5.25	3.1	0.29	96.14	61
F2	699.35	5.98	4.2	0.46	99.21	53
F3	697.31	5.25	3.9	0.51	98.34	42
F4	698.40	5.64	3.5	0.64	95.10	40
F5	695.67	5.89	3.4	0.60	97.34	35
F6	696.35	5.22	4.0	0.57	99.51	26
F7	698.72	5.81	3.4	0.39	97.32	53
F8	699.10	5.24	3.9	0.42	98.34	49
F9	697.64	5.98	3.6	0.37	98.47	43

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 206 nm.

Table 4: *In vitro* dissolution data for formulation F1-F9

TIME (MIN)	% OF DRUG RELEASE								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
5	9.23	11.69	15.38	10.61	12.81	16.62	10.15	13.81	14.81
10	26.86	29.06	30.81	22.81	32.61	22.49	16.99	18.73	34.82
15	38.94	53.89	52.89	32.89	58.01	35.28	29.87	42.24	46.02
20	52.62	68.03	79.32	46.09	79.86	68.62	60.12	69.06	63.19
30	63.25	72.81	80.67	61.86	82.09	82.84	77.59	79.01	82.81
45	70.98	87.22	95.23	72.64	91.69	99.39	83.63	86.89	94.34

From the table it was evident that the formulation prepared with Poloxamer 188 were showed good drug release i.e., F3 formulation (95.23%) in higher concentration of blend i.e. 150mg. Formulations prepared with Croscarmellose sodium showed good drug release i.e., 99.39 % (F6 formulation) in 150 mg concentration. When increase in the concentration of Croscarmellose sodium drug release increased. Formulations prepared with Sodium-starch glycolate showed maximum drug release i.e., 94.34 % (F9 formulation) at 45 min in 150 mg of blend. Among all formulations F6 formulation considered as optimized formulation which showed maximum drug release at 45 min i.e., 99.39 %. Croscarmellose sodium showed good release when compared to Poloxamer 188 and Sodium-starch glycolate. Finally concluded that F6 formulation contains Croscarmellose sodium was optimized formulation.

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Drug-Excipient compatibility studies by FTIR studies

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

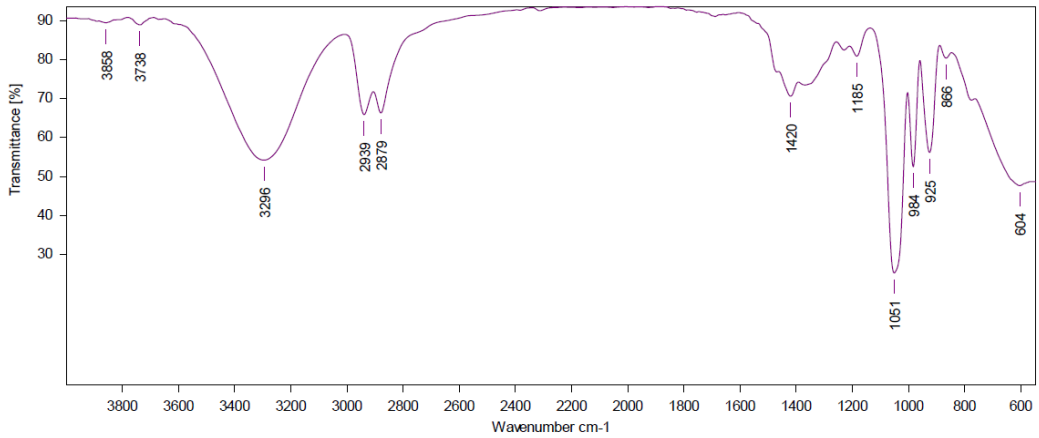

Fig 2: FTIR spectra of pure drug

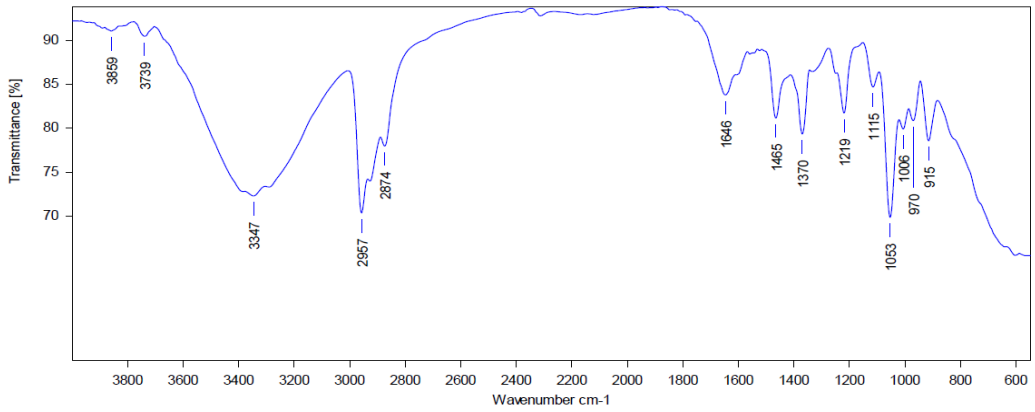

Fig 3: FTIR spectra of optimized formulation

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Piracetam and excipients used in the preparation of different Piracetam immediate Release formulations. Therefore the drug and excipients are compatible to form stable. Formulations under study, The FTIR spectra of Piracetam and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible.

CONCLUSION

The present study was aimed at developing immediate release tablet of Piracetam by using combination of surfactants such as Poloxamer188, Croscarmellose sodium, Sodium-starch glycolate and Sodium Lauryl Sulfate, and other such Avicel pH102, Talc by using direct compression technique. The immediate release tablets were evaluated for physicochemical parameter like thickness, hardness, weight variation, friability and *in-vitro* drug release. The *in-vitro* drug release study was found that optimized formulation F6 show immediate drug release within 45 minutes up to 99.39%. The independent variables exhibited a good response on the dependent variables to produce an effective formulation. Thus, the present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy, and patient compliance.

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