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Research

Formulation and Evaluation of Topiramate Immediate Release Tablets

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Abstract

The aim of the present study is to develop and evaluate the immediate release tablet of Topiramate by direct compression method. The super disintegrant Khaya gum, Kyron T-314 and Poloxomer 188were used for immediate release of drug from tablet. The precompression blends of Topiramate were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The precompression blend of all the batches indicates good to fair flowability, compressibility and were compressed into tablets. The formulated tablets were evaluated for various quality control parameters. The pure drug and super disintegrant formulations were subjected to FTIR studies, the results were showed that there is no interaction between the drug and excipients. All formulation showed compliances with Pharmacopoeial standards. The study reveals that formulations prepared by direct compression F3 exhibits highest dissolution using Kyron T-314 showed faster drug release 98.51%.

Keywords: Topiramate, super disintegrant, Immediate release tablet.

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 Super disintegrants 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]

Pharmacokinetics

It is the study of absorption, distribution, metabolism and excretion. After absorption, drug attains therapeutic level and therefore elicits pharmacological effect, so both rate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution is fast. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increase.

Pharmacodynamic[9]

- ✓ Drug reception interaction impaired in elderly as well as in young adult due to undue development of organ.
- ✓ Decreased ability of the body to respond reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin.
- ✓ Decreased sensitivity of the CVS to α-adrenergic agonist and antagonist.
- ✓ Immunity is less and taken into consideration while administered antibiotics.
- ✓ Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline
- ✓ shows increased sensitivity to barbiturates.
- ✓ Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed.
- ✓ Research workers have clinically evaluated drug combination for various classes cardiovascular agents, diuretics, anti-hypertensive etc. for immediate release dosage forms. The combination choice depends on disease state of the patient.

Merits[15]

1. Unit dose system and Long shelf life.
2. Cost effective.
3. Improved stability, bioavailability.
4. Accuracy and uniformity of drug content.
5. More Economic and Ease of administration.
6. Tastelessness and Elegance.
7. Patient compliance.
8. They are in general the easiest and cheapest to package.
9. Optimal drug dissolution and hence, availability from the dosage form for absorption consistent with intended use.

Demerits[15]

1. Posses swallowing difficulty.
2. Onset of action is slow and depends on disintegration and dissolution. Some drugs resistcompression, due to their amorphous nature or low-density.
3. Drugs having bitter taste, objectionable odor or drugs that are sensitive to oxygen mayrequire encapsulation or coating of tablet Bioavailability problems.
4. Chance of GI irritation caused by locally high concentrations medicaments.

Desired Criteria For Immediate Release Drug Delivery System

Immediate release dosage form shouldInthe case of solid dosage it should dissolve or disintegrate in the stomach within ashort 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 sensitivity 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.

Other Excipients

Excipients balance the properties of the actives inimmediate release dosage forms. This demands a thorough understanding of the chemistry of these excipients toprevent interaction with the actives. Determining the costof these ingredients is another issue that needs to beaddressed by formulators. The role of excipients isimportant in the formulation of fast-melting tablets. Theseinactive food-grade ingredients, when incorporated in theformulation, impart the desired organoleptic properties andproduct efficacy. Excipients are general and can be usedfor a broad range of actives, except some actives thatrequire masking agents.

Bulking Materials

Bulking materials are significant in the formulation of fast melting tablets. The material contributes functions of adiluent, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose)and starch hydrolystate for higher aqueous solubility and good sensory perception. Mannitol in particular has high aqueous solubility and good sensory perception. Bulk ingagents are added in the range of 10 percent to about 90percent by weight of the final composition.

Emulsifying Agents

Emulsifying agents are important excipients for formulating immediate release tablets they aid in rapid disintegration and drug release. In addition, incorporating emulsifying agents is useful in stabilizing the immiscibleblends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast-tablet formulation, including alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These agents can be incorporatedin the range of 0.05 percent to about 15 percent by weight of the final composition.

Lubricants

Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

Flavours and Sweeteners

Flavours and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients. Both natural and synthetic flavours can be used to improve the organoleptic characteristic of fast-melting tablets. Formulators can choose from a wide range of sweeteners including sugar, dextrose and fructose, as well as nonnutritive sweeteners such as aspartame, sodium saccharin, sugar alcohols and sucralose. The addition of sweetenerscontributes a pleasant taste as well as bulk to the composition.

Super Disintegrants

A disintegrant is an excipient, which is added to a tablet orcapsule blend to aid in the break up of the compacted masswhen it is put into a fluid environment.

Advantages

1. Effective in lower concentrations
2. Less effect on compressibility and flowability
3. More effective intragranularly

Some super disintegrants are

1. Sodium Starch Glycolate (Explotab, primogel) used in concentration of 2-8 % & optimum is 4%.

Mechanism of Action: Rapid and extensive swelling with minimal gelling. Microcrystalline cellulose (Synonym: Avicel, celex) used in concentration of 2-15% of tablet weight. And Water wicking

2. Cross-linked Povidone or Crospovidone (Kollidone) used in concentration of 2-5% of weight of tablet. Completely insoluble in water. Mechanism of Action: Water wicking, swelling and possibly some deformation recovery. Rapidly disperses and swells in water, but does not gel even after prolonged exposure. Greatest rate of swelling compared to other disintegrants. Greater surface are ato volume ratio than other disintegrants.

3. Low-substituted hydroxyl propyl cellulose, which is insoluble in water. Rapidly swells in water. GradesLH-11 and LH-21 exhibit the greatest degree of swelling. Certain grades can also provide some binding properties while retaining disintegration capacity. Recommended concentration 1-5%

4. Cross linked carboxy methyl cellulose sodium(Ac-Di-sol) Croscarmellose sodium:[9]

Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling. Effective Concentrations: 1-3% Direct Compression, 2-4%Wet Granulation.

MATERIALS

Topiramate-Procured From zyduscadila ahmedabad, India. Provided by SURA LABS, Dilsukhnagar, Hyderabad, Kyron T-314-Research Lab Fine Chem Industries, Mumbai, Khaya gum-Research Lab Fine Chem Industries, Mumbai, Poloxomer 188-Research Lab Fine Chem Industries, Mumbai, MCC-Shakti Chemicals, Mehsana, India, Aspartame-Merck Specialities Pvt Ltd, Mumbai, India, Mg stearate-S. D. Fine Chemicals Ltd., Mumbai, India, Talc-S. D. Fine Chemicals Ltd., Mumbai, India

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 10 1000ml of distilled water and mixed.

Preparation of pH 6.8 Phosphate buffer: Accurately measured 250ml of 0.2M potassium Dihydrogen otho 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 Topiramate

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 263 nm. Hence all further investigation were carried out at the same wavelength.

b) preparation of Standard graph in pH 6.8 phosphatebeffer

100 mg of Topiramatewas dissolved in method 5ml , volumetric flask make upto 100ml of Phospatebeffer 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 263 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 further 5 minutes. The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

Table 1: Formulation of Immediate Release tablets

INGREDIENTS	FORMULATION CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Topiramate	25	25	25	25	25	25	25	25	25
Kyron T-314	15	30	45	-	-	-	-	-	-
Khaya gum	-	-	-	15	30	45	-	-	-
Poloxomer 188	-	-	-	-	-	-	15	30	45
MCC	97	82	67	97	82	67	97	82	67
Aspartame	4	4	4	4	4	4	4	4	4
Mg stearate	5	5	5	5	5	5	5	5	5
Talc	4	4	4	4	4	4	4	4	4
Total WeightOf Tablet (mg)	150	150	150	150	150	150	150	150	150

Total weight of tablets = 150 mg

The tablets were prepared by using 7mmflat surfaced punch. The hardness of the tablets was maintained as 4.0-4.9 kg/cm^2.

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 263nm.

Calibration curve of Topiramate

The standard curve of Topiramate was obtained and good correlation was obtained with R^2 value of 0.998, the medium selected was pH 6.8 phosphate buffer.

Table 2: Standard graph values of Topiramate at 263 nm in pH 6.8 phosphate buffer

Copncentration (µg/ml)	Absorbance
0	0
5	0.161
10	0.301
15	0.435
20	0.566
25	0.698

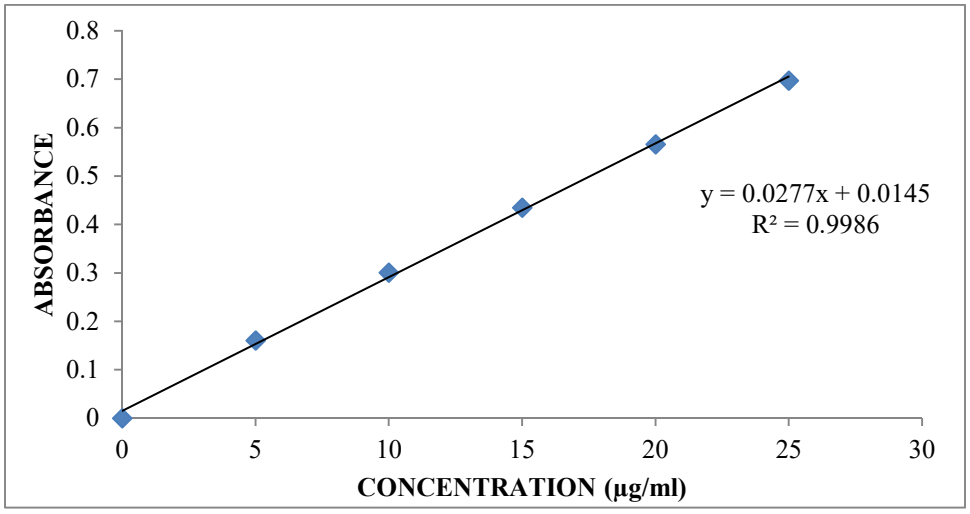

Fig 1: Standard curve of Topiramate

Evaluation

Characterization of precompression blend

The precompression blend of Topiramate were characterized with respect to angle of repose , bulk density , tapped densiy , Carr's index and Hausner's ratio. Angle of repose was less than 28.68˚, Carr's index values were less than 15.5 for the precompression blend of all the batches indicating good to fairfloability and compressibility. Hausner's ratio was less than 1.21 for all batches indicating good flow properties.

Table 3: 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
F1	26.76±1.2	0.526±1.8	0.612±1.6	14.0±0.02	1.16±0.1
F2	27.54±2.5	0.662±1.2	0.763±1.3	13.23±0.1	1.15±0.05
F3	24.65±2.5	0.695±1.5	0.823±0.8	15.5±0.08	1.18±0.1
F4	22.9±1.4	0.672±1.2	0.742±1.2	12.2±0.1	1.21±0.2
F5	28.3±2.2	0.643±2.1	0.624±0.7	14.2±0.9	1.11±0.2
F6	24.84±0.4	0.654±1.6	0.755±1.4	13.12±1.8	1.12±0.06
F7	28.68±0.8	0.782±1.2	0.869±0.8	11.0±1.2	1.11±0.2
F8	24.68±1.2	0.560±0.5	0.631±1.2	11.25±0.15	1.12±0.08
F9	25.16±0.8	0.628±2.5	0.714±1.6	14.27±0.12	1.17±0.5

All the values represent n=3

Evaluation of tablets

Physical evaluation of Topiramateimmediate 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 4.0-4.9 kg/cm^2 and the friability values were < than 0.67 % indicating that the tablets were

compact and hard. The thickness of the tablets ranged from 3.12- 3.96 cm. All the formulations satisfied the content of the drug as they contained 95.41-99.82 % of Topiramate 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 4: Physical evaluation of Topiramate

Formulation code	Average Weight (mg)	Thickness (cm)	Hardness (Kg/cm^2)	Friability (%)	Content Uniformity(%)	Disintegration Time (Sec)
F1	148.6	3.12	4.5	0.36	98.63	24
F2	150.2	3.96	4.3	0.52	97.53	65
F3	147.5	3.58	4.9	0.41	99.82	19
F4	149.3	3.75	4.1	0.53	95.41	35
F5	147.2	3.64	4.8	0.67	98.65	47
F6	149.8	3.33	4.5	0.20	99.20	31
F7	148.7	3.21	4.1	0.19	97.14	56
F8	146.3	3.82	4.6	0.49	99.72	39
F9	148.2	3.51	4.0	0.34	21.86	24

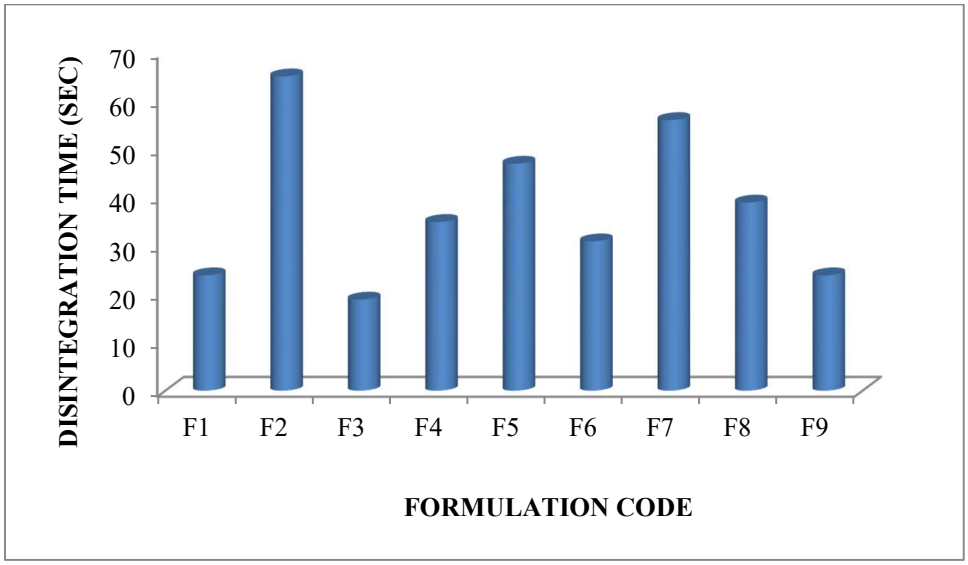

Fig 2: Disintegration Test (Sec)

***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 263 nm.

Table 5: *In vitro* 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	21.85	28.12	20.11	15.69	19.24	25.19	14.53	24.12	29.72
10	39.31	39.54	26.39	26.14	27.10	37.34	29.14	40.96	38.66
15	52.92	43.71	46.81	31.82	39.65	49.81	36.50	49.22	45.18
20	66.23	60.20	65.22	58.75	57.23	63.17	48.24	55.71	61.28
25	75.92	72.41	78.64	62.67	72.81	71.58	58.98	67.38	73.36
30	79.67	84.93	83.28	73.82	89.90	78.31	68.40	75.52	83.17
45	85.31	93.25	98.51	89.92	98.12	89.39	89.27	91.73	96.10

From the table it was evident that the formulation prepared with Kyron T-314were showed good drug release i.e., F3 formulation (98.51%) in higher concentration of Blend i.e 45 mg.Formulations prepared with Khaya gum showed good drug release i.e., 98.12 %

(F5 formulation) in 30 mg concentration. When increase in the concentration of Khaya gum drug release decreased.Formulations prepared with Poloxomer 188showed maximum drug release i.e., 96.10% (F9 formulation) at 45 min in 45 mg of blend. Among all formulations F3 considered as optrimised formulation which showed maximum drug release at 45 min i.e., 98.51 %. Kyron T-314showed good release when compared to Khaya gum. Finally concluded that F3 formulation contains Kyron T-314 was optimized formulation.

Drug-Excipient compatibility studies by FTIR studies

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

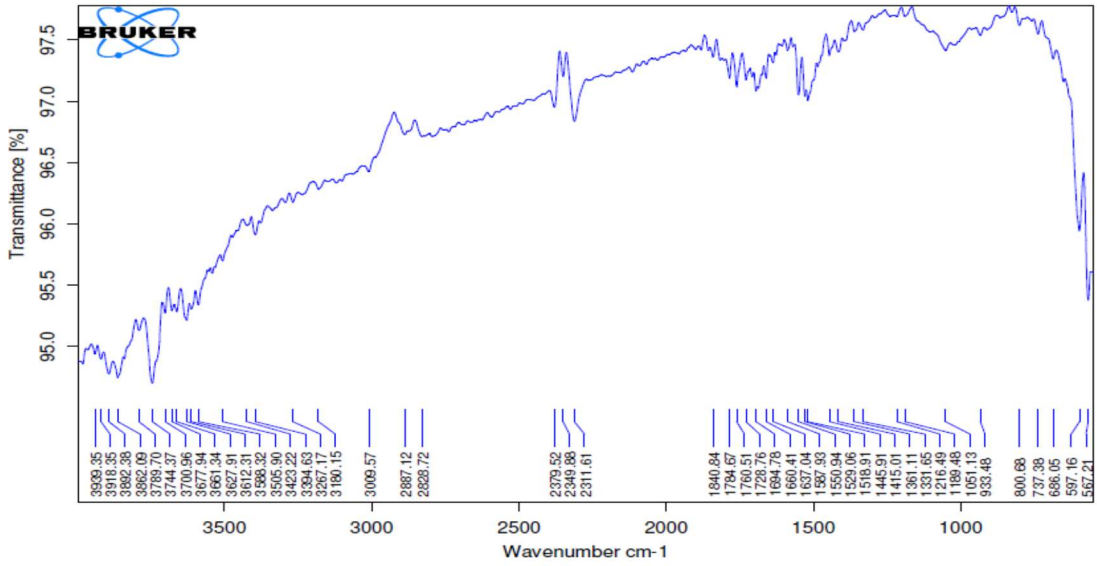

Fig 3: FTIR spectra of pure drug

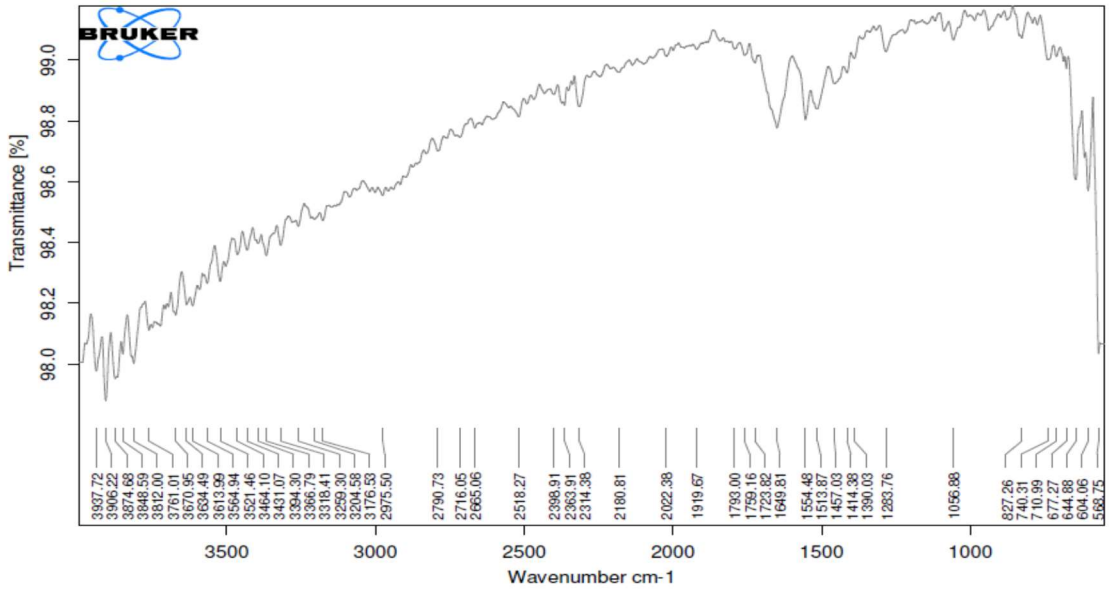

Fig 4: FTIR spectra of optimized formulation

From the above studies it was found that there was no shifting in the majorpeaks which indicated that there were no significant interactions occurred between the Topiramate and excipients used in the preparation of different Topiramate Immediate Release formulations. Therefore the drug and excipients are compatible to form stable. Formulations under study, The FTIR spectra of Topiramate 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 doses not have any interactions. Hence they were compatible.

CONCLUSION

Preformulation studies of Topiramate were performed; the FT-IR analysis revealed that the super disintegrants and excipients used were compatible with Topiramate Immediate release tablets of Topiramate is to be prepared by direct compression technique using super disintegrants, namely Khaya gum, Kyron T-314 and Poloxomer 188.The formulated tablets were evaluated for various quality control parameters. The tablets were passed all the tests. Among all the formulations F3 formulation containing drug and Kyron T-314 (45mg concentration) showed maximum and good result that is 98.51% drug release in 45 min. Hence from dissolution data it was evident that F3 formulation is the better formulation. Formulation containing Kyron T-314 as super disintgrants is fulfilling all the parameters satisfactorily. It has shown excellent *in vitro* drug release compared to other super disintegrants.

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