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

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Abstract:

Among the different routes of administration, the oral route of administration continues to be the most preferred route due to various advantages including ease of ingestion, avoidance of pain, versatility and most importantly patient compliance. The different dosage forms include tablets and capsules. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer and lead to better patient compliance. The present work involves the formulation development and in-vitro evaluation of immediate release Ambrisentan tablets. First Pre-formulation studies were carried out such as FTIR, bulk and tapped density, hounars ratio, Carr's index, the angle of repose etc. Then the tablets were prepared by direct compression using super disintegrating agents (Kyron T-314, Sodium Starch Glycolate and Crospovidone). All formulation showed compliances with Pharmacopoeial standards. The study reveals that formulations prepared by direct compression F5 formulation exhibits highest dissolution using Sodium Starch Glycolate showed faster drug release 100.07 %.

Key words: *Ambrisentan, superdisintegrant, Kyron T-314, Sodium Starch Glycolate and Crospovidone and Immediate release tablet.*

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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]

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.

Demerits: [15]

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

Desired 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 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 to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fast-melting tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

Bulking Materials:

Bulking materials are significant in the formulation of fastmelting tablets. The material contributes functions of a diluent, 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. Bulking agents are added in the range of 10 percent to about 90 percent 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 immiscible blends 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 non nutritive sweeteners such as aspartame, sodium saccharin, sugar alcohols and sucralose. The addition of sweeteners contributes a pleasant taste as well as bulk to the composition.

Super Disintegrants:

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

MATERIALS:

Ambrisentan Provided by SURA LABS, Dilsukhnagar, Hyderabad. ,Kyron T-314 Merck Specialities Pvt Ltd ,Sodium Starch Glycolate

Merck Specialities Pvt Ltd ,Crospovidone Merck Specialities Pvt Ltd ,Sodium saccharin Merck Specialities Pvt Ltd ,Mg stearate Merck Specialities Pvt Ltd ,Talc Merck Specialities Pvt Ltd ,MCC Merck Specialities Pvt Ltd

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 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.

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

Analytical method development for Nebivolol hydrochloride:

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

b) Preparation of Standard graph in pH 6.8 phosphate buffer100 mg of Ambrisentan was dissolved in methanol 5ml, volumetric flask make up to 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 10, 20, 30, 40 and 50µg/ml respectively. The absorbance was measured at 270 nm by using a UV spectrophotometer. 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.

INGREDIENTS	FORMULATION CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ambrisentan	5	5	5	5	5	5	5	5	5
Kyron T-314	10	20	30	-	-	-	-	-	-
Sodium Starch Glycolate	-	-	-	10	20	30	-	-	-
Crospovidone	-	-	-	-	-	-	10	20	30
Sodium saccharin	8	8	8	8	8	8	8	8	8
Mg stearate	5	5	5	5	5	5	5	5	5
Talc	4	4	4	4	4	4	4	4	4
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight of tablet (mg)	60	60	60	60	60	60	60	60	60

Table 1: Formulation of Immediate Release tablets

Total weight of tablets = 60 mg

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 270nm.

Calibration curve of Ambrisentan:

The standard curve of Ambrisentan 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 Ambrisentan at 270 nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
10	0.129
20	0.245
30	0.367
40	0.487
50	0.587

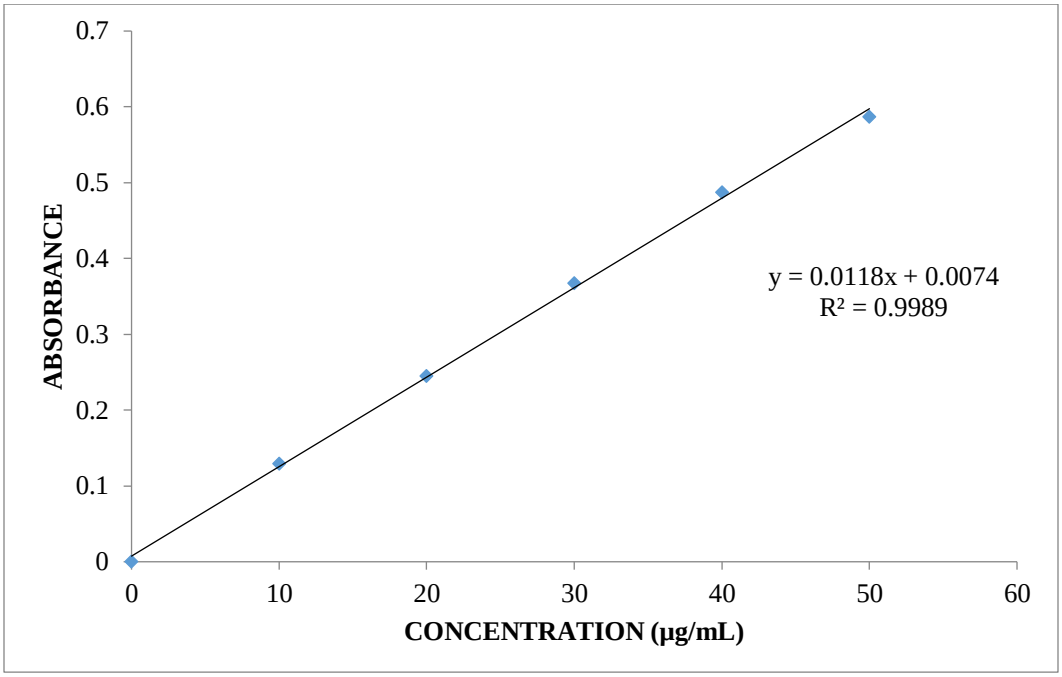

Fig1: Standard curve of Ambrisentan

Characterization of precompression blend:

Table3: 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	25.23	0.515	0.598	13.88	1.161
F2	23.25	0.525	0.61	13.934	1.162
F3	24.62	0.535	0.609	12.151	1.138
F4	24.56	0.512	0.587	12.777	1.146
F5	25.72	0.499	0.574	13.066	1.15
F6	24.3	0.512	0.582	12.027	1.137
F7	27.8	0.502	0.572	12.238	1.139
F8	25.54	0.518	0.586	11.604	1.131
F9	26.32	0.486	0.564	13.83	1.16

All the values represent n=3

Quality control parameters for tablets:

Table4: *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	46.83	53.16	57.32	58.43	64.91	68.10	45.15	51.78	55.61
10	53.92	57.27	62.15	69.52	72.64	75.29	58.99	64.12	69.52
15	66.68	68.51	70.92	74.01	81.20	88.35	69.16	73.59	78.90
20	70.15	72.73	75.80	80.10	86.09	90.63	75.29	78.60	85.13
25	85.29	77.96	80.12	87.28	90.60	95.89	80.31	86.14	92.05
30	89.70	92.32	95.05	92.36	95.14	99.16	87.90	91.22	94.34
45	93.54	96.18	97.73	95.62	100.07		90.56	95.63	97.28

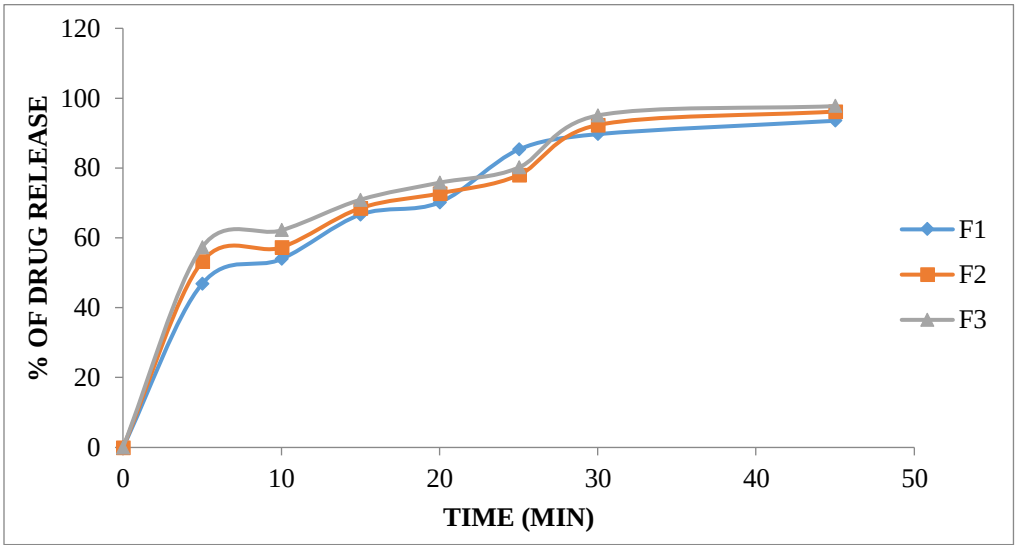

Fig 2: *In vitro* dissolution data for formulation F1-F3

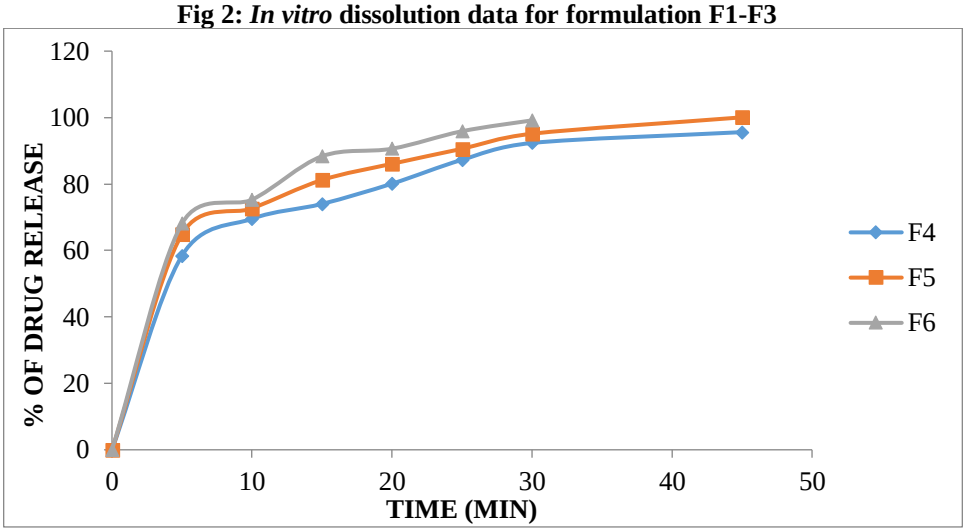

Fig 3: *In* vitro dissolution data for formulations F4-F6

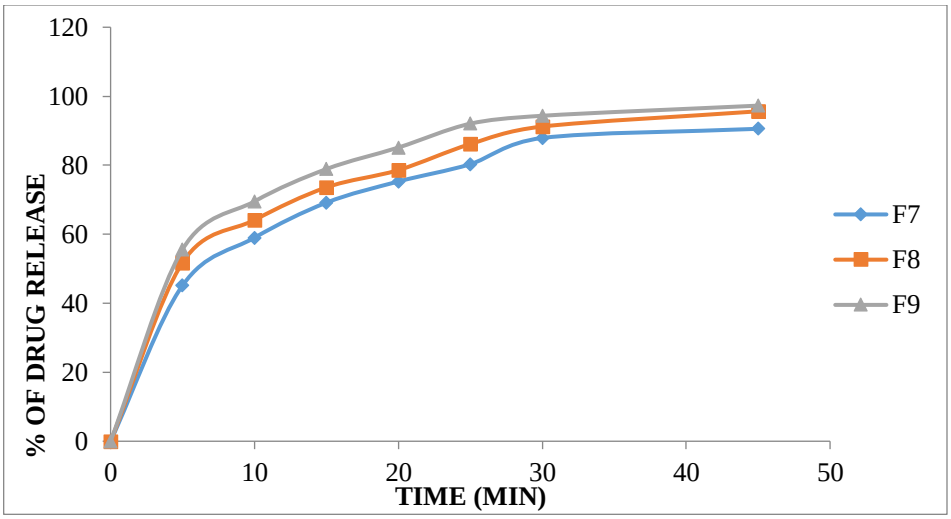

Fig 4: *In vitro* dissolution data for formulations F7-F9

Table5 : Physical evaluation of Ambrisentan

Formulation code	Weight variation (mg)	Thickness (cm)	Hardness (Kg/cm^2)	Friability (%)	Content Uniformity (%)	Disintegration Time (Sec)
F1	59.57	2.14	3.9	0.39	98.31	38
F2	58.65	2.65	3.6	0.51	96.86	29
F3	59.31	2.54	3.5	0.47	99.40	25
F4	56.90	2.29	3.7	0.54	98.73	32
F5	59.12	2.34	3.5	0.63	97.51	21
F6	60.09	2.61	3.0	0.28	98.92	23
F7	57.24	2.78	3.9	0.19	97.45	36
F8	58.65	2.34	3.4	0.24	98.61	30
F9	58.86	2.54	3.8	0.64	99.32	25

Drug – Excipient compatibility studies

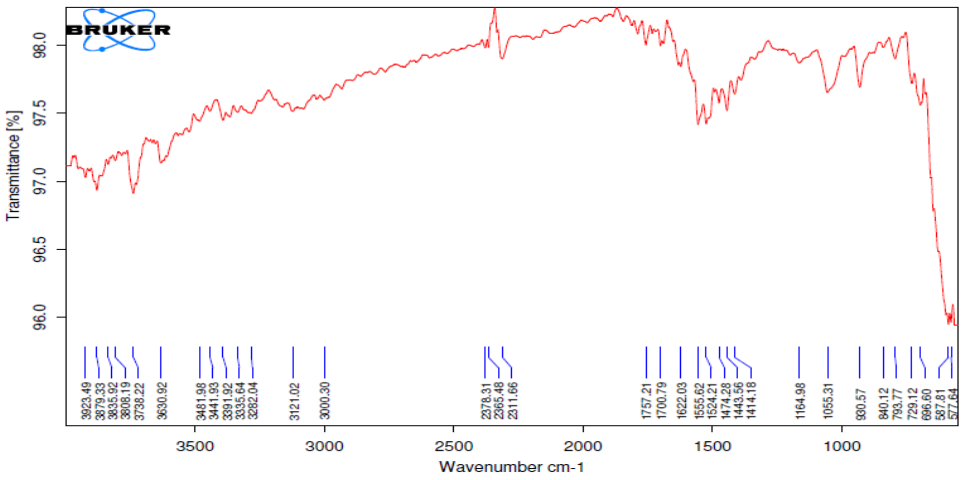

Fig 5: FTIR spectra of pure drug

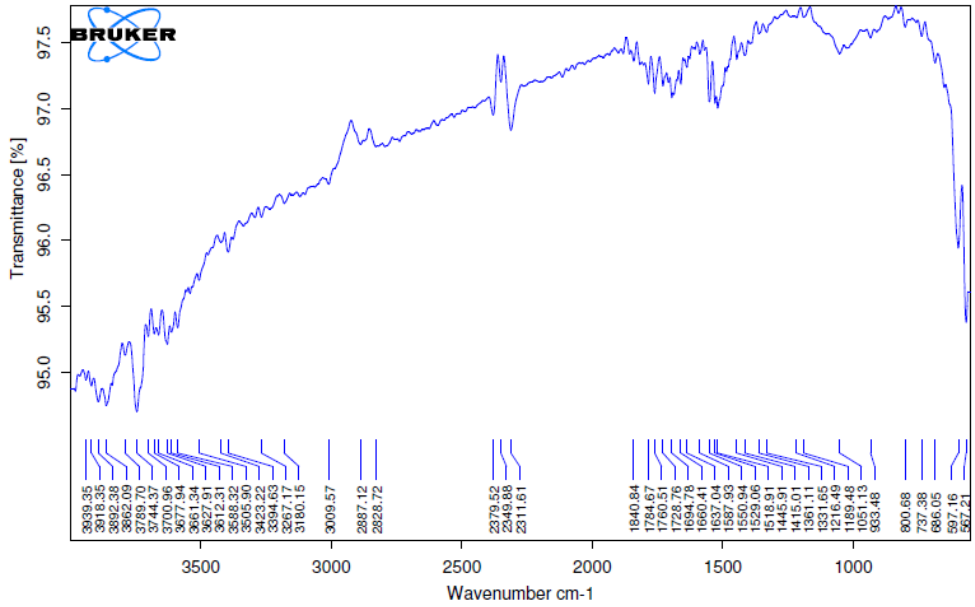

Fig 6: FTIR spectra of optimized formulation

CONCLUSION:

Immediate release tablets of Ambrisentan can be successfully prepared by direct compression techniques using selected super disintegrants (Kyron T-314, Sodium Starch Glycolate and Crospovidone) for the better patient compliance and effective therapy. FTIR studies revealed that there are incompatibilities between the drug and excipients used in the formulations. The precompression evaluation studies have shown that the powder blend has good flow properties and are suitable for direct compression. Post compression evaluation studies have shown that all the parameters were within the specifications for immediate release formulations. All the formulations developed formulation F5 was optimized based on the results of disintegration time and *in-vitro* dissolution profiles. It releases maximum of drug within 45mins there by the objective of increasing dissolution has been met by this formulation.

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