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Formulation And Evaluation Of Chewable Tablet Of Metformin HCl Using Stevia By Different Techniques

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Abstract: Stevia, a non-caloric sweetener and flavour enhancer. Stevia was originally available as a "dietary supplement".It is used as a weight loss aid; for treating diabetes, high blood pressure and heartburn; and for increasing the strength of the muscle contractions that pump blood from the heart.Its extracts are not absorbed by the digestive tract, so they do not add calories or affect blood glucose levels, making them a good addition to blood glucose levels. Therefore present work is an attempt to formulate an anti-diabetic drug metformin as a chewable tablet which helps to improve patient's adherence towards medication. Various evaluation parameters like thickness, hardness, friability weight variation and drug content of the formulations were found to be satisfactory. Release profile of the optimized formulations which were prepared by wet granulation technique showed satisfactory release within 30 minutes.The variation in the dissolution rate of Metformin chewable tablets made by different techniques were in the following order, direct compression< non-aqueous granulation< aqueous granulation. Chewable immediate release Metformin tabletDSC (Differential Scanning Calorimetry) and IR (Infra-red) studies showed no interaction between drug and excipients in optimized formulation.The optimized tablets found to be stable under accelerated conditions for a period of one month.
Key words: Formulation And Evaluation Of Chewable Tablet Of Metformin HCl Using Stevia By Different Techniques.

Introduction

Diabetes is a metabolic disorder characterized by high blood glucose either due to less production of insulin or because cells do-not respond to the insulin that is produced. Over the years there has been considerable success in diabetic research, whether it's the development of novel molecules like incretinmimetics or invasive drug delivery of insulin, last decade has seen it all and there has been plethora of strategies like these to better management of diabetes [1].

Steviahas been used as a natural sweetener since its extracts are not absorbed by the digestive tract and so they do not add calories or affect blood glucose levels, making them a good addition to blood glucose levels. Stevia also has mild anti-hyperglycemic, antihypertensive activity and its presence in the formulation may help in delaying the onset of hypertension which is common with type 2 diabetes [2].

Non-adherence to medication is potentially one of the most serious problems facing diabetes care delivery, particularly in type 2 diabetes. Intervention studies to improve adherence can be developed which include improved patient-centred education, health professional education [3].

This work is focussed on chewable Metformin HCl tablets using stevia. Diabetics need to limit their sugar intake because sugar and other carbohydrates from food cause a short-term increase in blood glucose levels. Commonly used sweetening agents in chewable tablet are carbohydrates and are not appropriate for diabetic people. Diabetics have to control their intake of sugar/sweets and psychologically they have more tendency towards sweets and thereby the chewable tablet may be more acceptable by the patients. Metformin chewable tablets formulation may provide more palatable and acceptable dosage form for diabetic patients and improve medication adherence.

Materials

Metformin HCl is was obtained from Aurobindopharma Ltd, Hyderabad, India; mannitol, lactose anhydrous were procured from merck Specialities Pvt. Ltd, Mumbai, India; Vanilla flavour and Avicel 101 were obtained from S d fine Chem Ltd, Mumbai, India; Aspartame was procured from Ozone International, Mumbai, India; stevia was obtained from Procarvit food products Pvt. Ltd, tamilnadu, India.

Tablet Formulation

Composition of different formulation batches of chewable metformin tablets are shown in table no.1. Formulations M 1- M3 were done by aqueous granulation method, M4 by non-aqueous granulation method and M5 by direct compression method.

Aqueous Granulation

Drug and excipients were blended in polybag for 2 min and sufficient amount of 10% PVP was added form dough mass. The mass was passed through sieve no. 12 to obtain raw granules, which were then dried in hot air oven at 50˚C for 30 min. After drying, the sieved granules were blended with stevia, flavouring agent and colouring agent, magnesium stearate and talc. The granule mixture were evaluated for flow property and were compressed using a single punch tableting machine (Cadmach machinery CO. Pvt. Ltd) equipped with 15mm round flat and plain punch to obtain required hardness.

Non-aqueous Granulation

The dry mixture of drug and excipient was granulated with 10% PVP in isopropyl alcohol solution and dried in the hot air oven at the temperature of 40-50˚C. The dried granules were passed through mesh no. 22; blended with required quantity of stevia. Colouring agent and flavouring agent were also added to the granules and blended for ten minutes. The above blend was lubricated with Magnesium stearate, Talc for two minutes. The powder blends was evaluated for the flow properties and compressed into tablets.

Direct Compression

Drug and excipients(avicel, mannitol, starch, stevia)were sifted and blended for ten minutes in poly bag. Flavouring agent and colouring agent was added to the above mixture. Finally the above blend was lubricated with Magnesium stearate, talc for two minutes. The powder blend was evaluated for the flow properties. The evaluated blend was compressed into tablets.

Table.1: Composition of Metformin HCl chewable tablets

Ingredients (mg/tablet)	Formulation				
	M-1	**M-2**	**M-3**	**M-4**	**M-5**
Metformin HCl	**500.0**	**500.0**	**500.0**	500.0	500.0
Mannitol	**100.0**	**100.0**	**150.0**	150.0	150.0
Lactose anhydrous	**100.0**	**100.0**	**---**	---	---
Avicel 101	**75.0**	**75.0**	**100.0**	100.0	100.0
Stevia	**---**	**15.0**	**20.0**	20.0	20.0
Aspartame	**15.0**	**---**	**---**	---	---
Vannilin/ raspberry flavour	**5.0**	**5.0**	**5.0/5.0**	5.0/5.0	5.0/5.0
PVP 10%	**q.s**	**q.s**	**q.s**	q.s	---
Magnesium stearate	**5.0**	**5.0**	**5.0**	5.0	5.0
Talc	**5.0**	**5.0**	**5.0**	5.0	5.0
Raspberry colour	**---**	**---**	**0.5**	0.5	0.5

*M-1, 2, 3 –aqueous granulation, *M-4- non aqueous granulation
*M-5 - direct compression, * Colour was not used for formulations with vanilla flavour

Drug excipients compatibility studies

Literature survey [4] shows there as such no interaction between metformin and excipients selected for our formulation and in addition the physical mixture may not show any incompatibility under normal storage conditions. So preformulation screening of drug-excipient interaction was not carried out in our research work. But the final optimized formulations were screened for drug- excipient interaction (DSC and IR).

Characterization of granules

Prior to compression, blends of were evaluated for their characteristic parameters, such as angle of repose, bulk density, tapped density, compressibility index and Hausner Ratio. Carr's index was calculated from the bulk and tapped densities using a digital tap density apparatus (Electrolab Ltd, india).

Tablet Characterization[5]

The tablets were characterized immediately after preparation. The weight variation of the tablets was evaluated on 20 tablets using an electronic balance (Essae-Teraoka Ltd. Bangalore). Friability was determined using 10 tablets in a Roche friabilator for 4 minutes at a speed of 25 rpm (rotations per minute). The hardness of 10 tablets for each formulation batch was evaluated using a Monsanto hardness tester (Secor India PVT ltd). The thickness of the tablets was measured on 10 tablets with VernierCalipers (Mitutoyo, Japan).

Drug content: For determination of drug content, three tablets were crushed and powder was dissolved in 50ml of 0.1N buffer. The solution was then filtered through whatmann (No.1) filter and analysed spectrophotometrically at 233 nm after sufficient dilution with buffer. Drug content was calculated from calibration curve of metformin in the same buffer.

Disintegration [6, 7]

This test initially may not appear appropriate for chewable tablets as these tablets are to be chewed before being swallowed. However, patients, especially pediatric and geriatric, have been known to swallow these chewable dosage forms. This test would thus indicate the ability of the tablet to disintegrate and still provide the benefit of the drug if it is accidentally swallowed. Tablets should preferably pass the USP disintegration test for uncoated tablets.

Dissolution studies [6]

Chewable tablets should preferably be tested in two forms: intact (in case the dosage form is accidentally swallowed) and partially crushed (to simulate chewing). The study was carried in 900ml of 0.1N HCl for duration of 2 hours (rpm is set to 100); the temperature was maintained at 37±0.5˚C. Aliquots of 5.0 ml were withdrawn at specific time intervals. At each time of withdrawal, 5ml of fresh corresponding medium pre-warmed to 37 ± 0.5°C was replaced into the dissolution flask.

Stability studies [8]

The optimized tablet formulation were packed in the aluminium foil and kept in stability chamber at 40˚C and 75% RH (relative humidity) for a period of one month and evaluated for physical appearance and drug content.

Results And Discussion

Characterization of powder flow properties

The compressibility index for all the formulations was found to be within the range 10-21, which indicates the good to fair flow properties, the flow properties were further analysed by determining the angle of repose, which were within the range of 30˚. The Hausner's ratio for all the granules formulated are less than 2%, indicating free flow property [table 2].

Table.2: Physical characteristics of granules of Metformin HCl blend

Batch no.	Bulk density (g/cc)	Tapped density (g/cc)	Carr's compressibility index (%)	Angle of repose	Hausner's ratio
M-1	0.3645	0.459	20	28.5±0.12	1.25
M-2	0.317	0.355	10.7	28.1±0.20	1.12
M-3	0.625	0.714	12.46	28.4±0.09	1.14
M-4	0.484	0.587	17.44	29.1±0.06	1.18
M-5	0.472	0.562	15.86	28.1±0.07	1.19

Physicochemical Evaluation Of Tablets

All the formulations showed similar thickness. Tablets from different formulations showed hardness in the range of 4-4.3 Kg/Cm^2. Usually for conventional tablets the friability value of 1% or less is desirable but for chewable tablets due to low hardness values the friability values up to 4% [6] are desirable,all formulations were well within the. All formulations passed the USP requirement in terms of weight variation and drug uniformity. All the formulations showed disintegration time below 15 min like conventional uncoated tablets [table 3].

Table.3: Physicochemical evaluation of Metformin chewable tablets

Batch no	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight Variation (%)	Drug content (%)	Disintegration Time (min)
M-1	5.22±0.04	4.3±0.17	2.10±0.20	99.67±0.09	97.5±1.05	13.5±0.5
M-2	5.21±0.02	4.23±0.05	2.07±0.35	99.56±0.11	98.13±0.7	13.5±0.5
M-3	5.20±0.03	4.5±0.11	2.87±0.12	99.12±0.09	97.23±0.45	13.4±0.7
M-4	5.20±0.02	4.03±0.11	3.89±0.09	99.34±0.12	98.12±0.62	12.3±0.3
M-5	5.20±0.02	4.06±0.11	3.91±0.14	99.54±0.04	99.12±0.5	10±0.2

All values are expressed as mean ± SD (n=3)

Release profile

Percentage cumulative drug release of all 5 formulations of Metformin chewable tablets were shown in table 4. The variation in the dissolution rate of Metformin chewable tablets made by different techniques were in the following order, direct compression< non-aqueous granulation< aqueous granulation.Formulation M-5 which was prepared by direct compression had cumulative drug release of 100% at 20 mins, and 99.35% at the end of 60 minsfor crushed and intact tablet respectively.Theformulations M-1, 2, 3, 4 have shown similar drug release for crushed and intact tablet i.e. 100% at the end of 30 mins and 2hrs respectively. Formulation M-4 has low hardness with high friability value. Formulation M-2 and M-3 have stevia as sweetening agent which might have beneficial effect than aspartame in M-1 formulation. Therefore formulation M-2 and M-3 were considered as optimized formulations.

Drug-Excipient compatibility studies:

a) Differential scanning calorimetry

The DSC thermograms of pure Metformin and optimised formulations M-2 and3 are shown in Fig.1, 2**.**Pure Metformin HCl shows sharp endotherm at 238.4˚C corresponding to its melting point/transition temperature. A slight lowering of melting point of M-2, 3 are observed.Mannitol and lactose which are polyhydroxy compounds might have physical interaction with the metformin and so a short deviation of melting point of metformin was observed.

b) Infrared spectroscopy

The optimized formulation did not produce major shift in peaks, indicating no interaction. The principal IR peaks of pure Metformin HCl and optimized formulations are shown in fig.4.

Thus the findings of DSC andFTIR spectrahave proved the compatibility between drug and excipients in our optimized formulations.

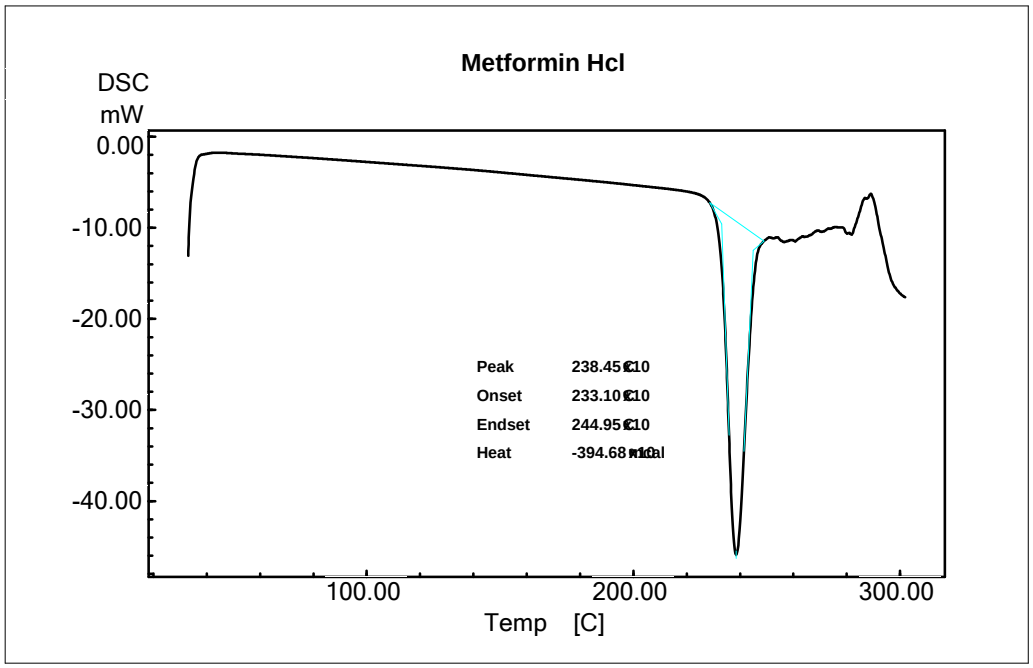

Fig.1: DSC Thermogram of pure Metformin HCl

Table.4: *In-vitro* release of metformin HCl from both intact and crushed tablets of formulations M-1, 2, 3, 4 and 5

Time in mins	% Cumulative Drug Release									
	M-1 (crushed)	**M-1 (intact tablet)**	**M-2 (crushed**	**M-2 (intact tablet)**	**M-3 (crushed)**	**M-3 (intact tablet)**	**M-4 (crushed)**	**M-4 (Intact tablet)**	**M-5 (crushed)**	**M-5 (intact tablet)**
0	0	0	0	0	0	0	0	0	0	0
5	31.17±0.95	18.34±1.57	31.08±1.42	22.78±1.51	30.23±1.2	12.34±2.23	40.32±1.34	18.45±0.78	41.6±1.46	21.84±0.95
10	51.62±1.33	28.95±1.45	51.38±1	26.06±0.25	52.04±0.98	27.34±0.89	61.45±0.56	26.67±1.12	61.81±1.73	33.02±1.78
20	80.95±1.46	34.33±0.48	81.26±0.93	32.17±0.87	78.98±1.45	33.45±1.07	85.78±2.34	32.90±0.45	98.03±2.06	51.05±1.07
30	100	47.11±0.77	100	44.70±1.28	100	42.34±0.55	100	42.56±2.33	---	74.11±1.9
40	---	57.97±1.80	---	63.46±0.98	---	60.45±1.34	---	65.43±1.49	---	80.22±2.61
50	---	67.65±0.77	---	70.46±0.67	---	71.20±0.88	---	71.12±0.45	---	93.99±1.87
60	---	72±0.85	---	77.74±1.68	---	78.33±1.77	---	78.67±1.21	---	99.35±0.89
75	---	75.73±1.50	---	81.13±1.08	---	84.89±0.45	---	84.14±0.78		
90	---	81.82±0.57	---	87.54±0.89	---	89.96±0.78	---	91.39±1.23		
120	---	93.07±1.46	---	96.35±2.23	---	95.23±1.65	---	100		

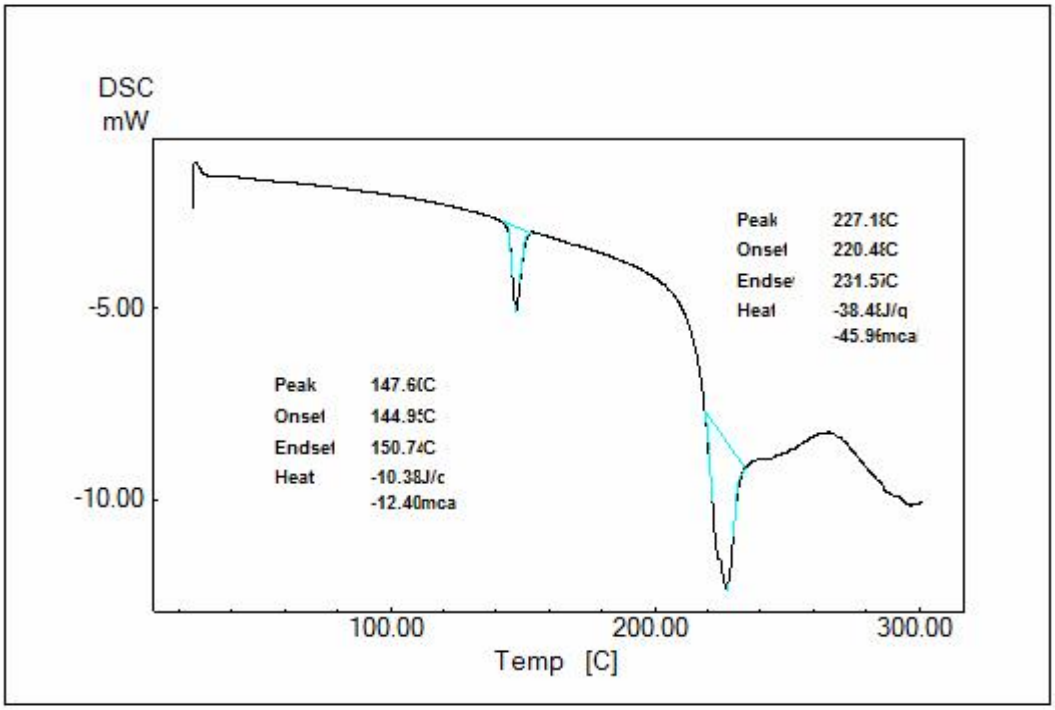

Fig.2: DSC Thermogram offormulation M-2

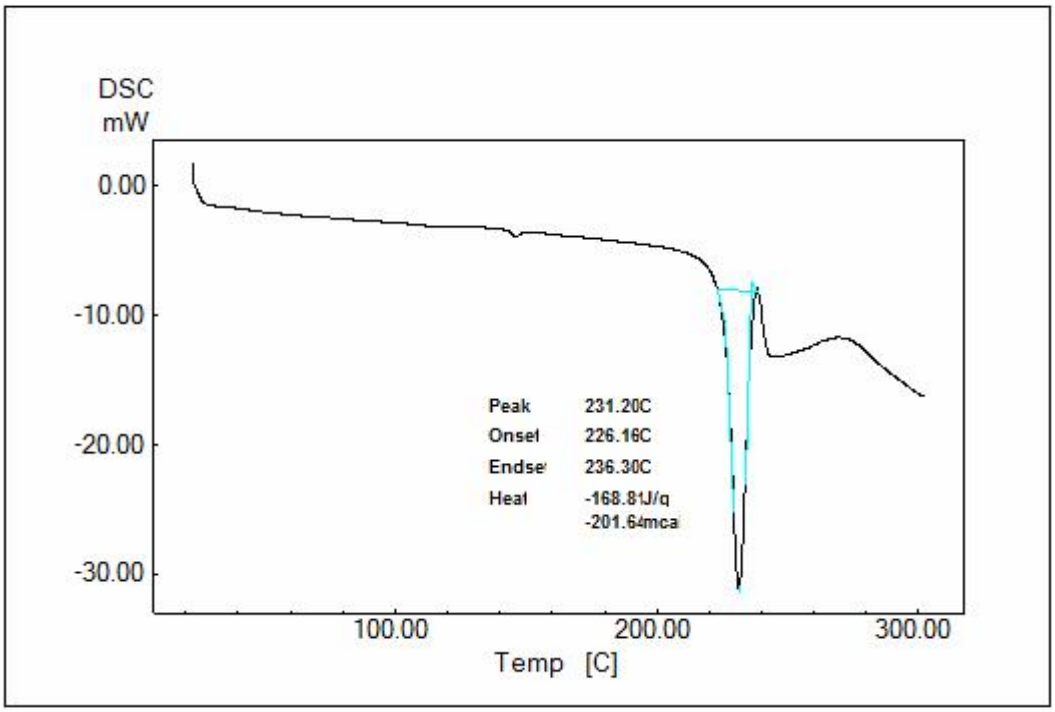

Fig.3: DSC Thermogramofformulation M-3

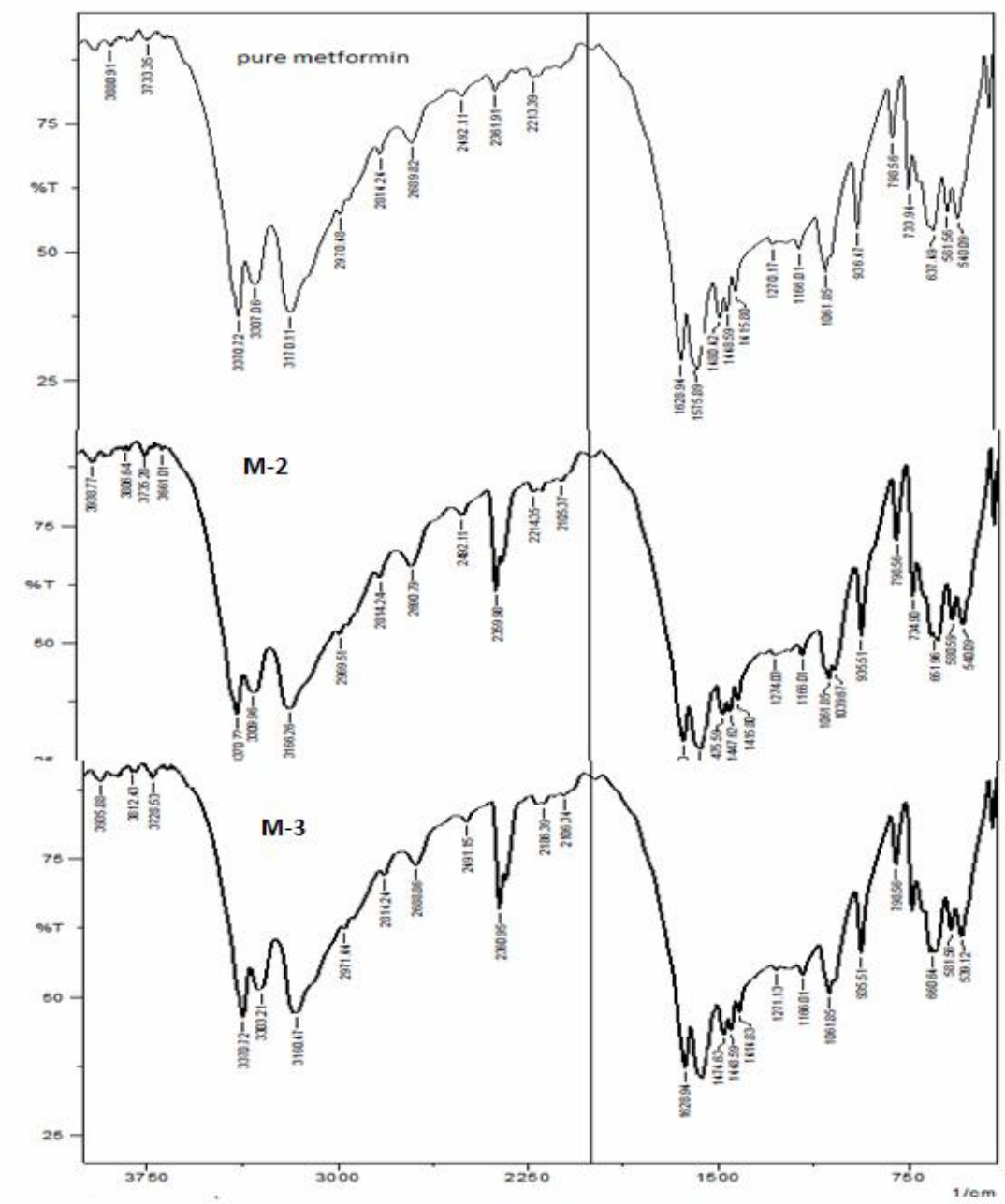

Fig.4:IR peaks of pure metformin HCl, formulation M-2 and M-3

Stability Studies

On storage under accelerated conditions the tablets did not show any physical changes. The percentage drug content of both immediate and sustained release optimized formulations is given in the table.5.

Table.5: Stability study data

Days	Percentage of drug release	
	M-2	M-3
0	97.5±1.05	98.13±0.7
15	97.5±0.95	98.02±0.54
30	97.2±0.76	98±0.43

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