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FORMULATION AND INVITRO EVALUATION OF AMLODIPINE BESYLATE ORAL DISINTEGRATING TABLETS

K. Rama Krishna*
Department of Pharmaceutics,
Pulipati Prasad College of Pharmaceutical sciences,
Affiliated to Kakatiya University, Warangal, Telangana state.

ABSTRACT
The aim of the present work is to design oral disintegrating tablet of Amlodipine besylate using superdisintegrants like cross povidone, cross carmellose sodium and sodium starch glycolate at concentrations of 5 – 20 %. sweetening agents and flavouring agents were added for better mouth feel. Oral disintegrating tablet of Amlodipine besylate were prepared by direct compression method. The prepared powdered blend of the formulations were evaluated for precompression properties like angle of repose, bulk density, tapped density, Hausner's ratio, Carr's compressibility index. The results showed that the powder blend has good flow properties. The prepared tablets were evaluated for post compression parameters like weight variation, thickness, hardness, wetting time, content uniformity, in vitro disintegrating time and friability. The results were found to be uniform within the pharmacopoeial limits. The effect of superdisintegrants on in-vitro release of drug has been studied. Among the 12 formulations tablets containing sodium starch glycolate (20%) showed excellent in-vitro disintegration time of 18 secs and complete drug release in 15 mins. FTIR & DSC studies were conducted to determine the compatibility between the drug and selected superdisintegrants. The studies confirmed that there is no evidence of interaction between the drug and superdisintegrants. It is concluded that Amlodipine besylate oral disintegrating tablets could be prepared by direct compression using selected superdisintegrants.

Keywords: *Amlodipine besylate, cross povidone, cross carmellose, sodium starch glycolate direct compression, orally disintegrating tablets.*

Address for correspondence:
K. Rama Krishna,
Pulipati Prasad College of Pharmaceutical sciences,
Pin 507 305.
Email ID: ramakrishnakavati@gmail.com

INTRODUCTION

Amlodipine besylate undergoes first pass effect and gets extensively metabolised in the liver when ingested orally. This necessitated in developing oral disintegrating tablets of amlodipine besylate. Oral route is the most widely used route of administration, because it offers advantages like convenience in self administration and easy to manufacture [1-2]. Orally disintegrating tablets has gained enormous demand and has significant impact on the patient compliance. Oral dispersible tablets are much appreciated by the people having difficulty in swallowing [3]. ODT"s can be conveniently given to paediatric, geriatric people, psychiatric patients and patients suffering with nausea, vomiting complications and motion sickness [4,5,6]. United States pharmacopoeia (USP) approved these dosage forms as ODTs and recently European Pharmacopoeia has used the term orodispersible tablet for tablets that gets readily disperses within 3 min in mouth prior to swallowing [7].

USFDA defined ODT as A solid dosage form containing medicinal active ingredient which disintegrates rapidly usually within seconds when placed in the buccal cavity. ODTs should disintegrate generally from few seconds to about a minute. [8]

Bioavailability of drugs can be increased when formulated as ODT due to absorption of drugs in oral cavity when formulated as Pregastric absorption of saliva containing dispersed drugs avoids first pass metabolism effect when compared to standard tablets that are meant to swallow [9-10].

ODT"s does not require water after oral administration and bitter drugs can be taste masked effectively rendering them to have pleasant mouth feel [11].

Amlodipine besylate is an antiretroviral drug of protease inhibitor class, used to treat human immunodeficiency virus (HIV). Amlodipine besylate can be given once-daily and is reported to have lesser effects on the patient's lipid profile - the amounts of cholesterol and other fatty substances in the blood. Like other protease inhibitors, it can also be given in combination with other HIV medications.

Amlodipine besylate is a long-acting 1, 4-dihydropyridine calcium channel blocker. It acts mainly on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, Amlodipine besylate prevents calcium-dependent myocyte contraction and vasoconstriction. Amlodipine is used in the treatment of hypertension and chronic stable angina. Amlodipine is slowly and completely absorbed from the gastrointestinal tract. Peak plasma concentrations are reached 6-12 hour following oral administration [12-13].

MATERIALS AND METHOD

Amlodipine besylate is obtained as gift sample from Aurobindo laboratories, hyd. Cross povidone, Cross carmellose sodium, Sodium starch glycolate are the superdisintegrants obtained from AVEB chemicals. Aerosil, Sweetener, Banana flavour, Talc, Magnesium stearate used are of analytical grade.

Direct compression method

Drug, superdisintegrants and other excipients were weighed accurately according to the formula and mixed in geometric proportions using a mortar and pestle. The mixture was passed through sieve no 30 and mixed thoroughly in a polythene bag for 10 mins. Polymer used were cross povidone (CP), cross carmellose sodium (CCS), sodium starch

glycolate (SSG) at different polymer concentrations like 5%,10%,15%, and 20%. Finally the powdered blend was compressed into tablets on a 16 station rotary punching machine with 6 mm round, flat faced punches. All the formulations were prepared by direct compression method shown in table-1.

PRECOMPRESSION PARAMETERS [14, 15]:

The micromeritic properties of the prepared powdered blend was evaluated for parameters like Angle of repose , Bulk density, Tapped Density, Compressibility index and hausner ratio.

EVALUATION OF TABLETS

Weight variation [16] of the tablets was determined by using electronic weighing balance. Hardness [17] of the tablets was measured by using Monsanto hardness tester. Thickness [17] of the tablets was determined by using digital vernier callipers. % Friability [17] of the tablets was measured by using Roche friabiliator which is rotated for 25 revolutions per minutes for 4 minutes.

Wetting Time [18]

Five circular tissue papers of 10 cm diameter are placed in a Petridish and 10 mL of waterwas added to it. Compressed tablets were carefully placed on the surface of the tissue paper. The time required for water to reach onto the upper surface of tablet was noted as a wetting time. The procedure was repeated on 6 tablets and mean values was recorded.

In-vitro Disintegration Test [16]

The test was performed on 6 tablets randomly using Labindia Tablet disintegration apparatus. 0.01N Hcl was used as a disintegration media. The time taken by the tablets to disintegrate completely was measured in seconds.

Drug content uniformity [16]

Six tablets were collected randomly and powdered using mortar and pestle. Equivalent weight of 100 mg of Amlodipine besylate was transferred into a 100 ml volumetric flask and dissolved using 0.01N Hcl. The solution was filtered and diluted suitably. Drug content was measured at λ max 246 nm using UV-spectrophotometer.

In-vitro drug release studies [16]

The in-vitro drug release studies of Amlodipine besylate from orally disintegrating tablets was carried out using USP dissolution test apparatus type-II (Paddle type) rotated at 50 rpm in 900 ml of dissolution medium 0.01N HCl and temperature was maintained at 37±0.5°C. At specified time intervals, 5 ml samples were collected and replaced with an equal volume of fresh prewarmed medium. Samples were diluted suitably and analyzed by using UVspectrophotometer at λ max 246 nm.

CHARECTERIZATION DRUG AND EXCIPIENT COMPATIBILITY

Differential scanning calorimetric studies (DSC) [19]

Thermal properties of pure drug Amlodipine besylate and the formulations were evaluated by Differential Scanning Colorimetry (DSC) using DSC 200 F3 instrument. The samples were placed in standard aluminium pans and sealed with a lid. Heating scans by 10k/min were applied with a nitrogen purge of 60ml/min over a temperature range of 00 to 450 ^{o}C. An aluminium pan was used as a reference. A quality equivalent to 2 mg of pure drug was used for the study.

Fourier transform infrared spectroscopy (FT-IR) [20]

The drug - excipients interaction were studied using Fourier transform infrared spectrophotometer (FTIR). IR spectra for drug and powdered tablets were recorded in a Fourier transform infrared spectrophotometer (FTIR 1615, Perkin

Elmer,USA) with Potassium Bromide (KBr) pellets.

RESULTS AND DISCUSSION

Precompression parameters

The prepared powder blend of the formulations was evaluated for micromeritic properties as per the reported procedure in IP. The angle of repose of the entire blend in all the formulations were found to be in the range 21^0 86"±1.06 to 34^0 29" ±1.03. The Bulk Density was found to be in the range of 0.319±0.14 to 0.421±0.07 and Tapped Density ranged from 0.441±0.06 to 0. 0.541±0.02 respectively. Percentage Compressibility index was found between 20.53±1.05 to 26±1.08. The Hauser ratio was ranged from 1.21±0.05 to 1.39±0.04.

Post compression parameters

The compressed tablets of different formulations were evaluated for various post compression parameters like weight variation, hardness, thickness, friability, Wetting time, Disintegration time and % drug content. All the formulated tablets of the formulations passed weight variation test within the pharmacopoeia limits. The weight of all the tablets was found to be uniform. Tablets mean thickness were uniform in all the formulations and were found to be in the range of 2.19 to 2.57 mm. The measured hardness of tablets of each batch ranged between 2.5 to 3.8 kg/cm2. The value of % Friability of each batch was found to be in the range of 0.41 % to 0.82% which ensures that the tablets can withstand to the mechanical shocks during transportation and handling. All formulations showed less than 1% (w\w) friability. % the wetting time of the formulation was found to be between 6.2 mins to 35 secs. The invitro disintegrating time was in the range of 3.1 mins to 18 secs. Wetting time and invitro disintegrating time was found to get decreased as the concentration of superdisintegrants was increased. Drug content of all the formulations were uniform and were found to be in the range of 98.5% to 99.8%.

% Invitro release of Amlodipine besylate from oral disintegrating tablets

The release rate of Amlodipine besylate from oral disintegrating tablets was determined using USP dissolution testing apparatus II (paddle type) at 50 rpm using 0.01 N HCl as dissolution medium. Amlodipine besylate oral disintegrating tablets were prepared by using super disintegrant like cross povidone, cross carmellose sodium, sodium starch glycolate. Drug release of Amlodipine besylate from all the formulations F1 to F4 ranged from 50.3 to 64.6% during the first 5 mins, it was between 80 and 98 % by 30 mins. . Drug release of Amlodipine besylate from all the formulations F5 to F8 ranged from 54.5 to 66.5% during the first 5 mins, formulation F8 showed complete drug release within 20 mins. Drug release of Amlodipine besylate from all the formulations F9 to F12 ranged from 61.8 to 83% during the first 5 mins, formulation F12 showed complete drug release within 15 mins. The release of Amlodipine besylate mainly depends upon the super disintegrant concentration. It was found that, increase in the content of superdisintegrants, increased the drug release shown in figures-1,2 &3.

Differential scanning calorimetry (DSC) Study:

DSC study was conducted on the pure drug and OD tablets. DSC thermogram of pure Amlodipine besylate showed sharp endothermic peak at 208.2 ^{0}C. Similar endothermic peak was obtained with the formulations containing Amlodipine besylate oro dispersible tablets at 207.1 ^{0}C. This clearly indicates that there is no interaction between the pure drug and superdisintegrants shown in figures 4 &5.

Fourier transforms infrared Radiation measurement (FT-IR)

FTIR study was performed on the selected formulation prepared with different superdisintegrants such as pure Amlodipine besylate and final dosage form. The spectrum peak points of the formulation were similar with that of the pure Amlodipine besylate, clearly indicating that there is no interaction within pure drug and superdisintegrants shown in figures 6 &7.

CONCLUSION

The present investigation of this study was undertaken with an aim to formulate and characterize oral disintegrating tablets of Amlodipine besylate using direct compression method with super-disintegrating agents. The results of micromeritic evaluation confirmed that the powder blend has good flow properties. Quality control test results were within the pharmacopoeial limits. It was concluded that the formulation F10 containing 15% crosspovidone was found to be promising showing disintegration time of 21 seconds, wetting time of 45 second and highest dissolution rate of 99.3% in 15 min when compared to other formulations. FTIR and DSC study confirmed that there is no drug-excipients interaction between Amlodipine besylate and excipients.

Table 1: Formulation development of Amlodipine besylate oral disintegrating tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Amlodipine besylate	10	10	10	10	10	10	10	10	10	10	10	10
CP	5	10	15	20	---	---	---	---	---	---	---	---
CCS	---	---	---	---	5	10	15	20	---	---	---	---
SSG	---	---	---	---	---	---	---	---	5	10	15	20
Lactose	65	60	55	50	65	60	55	50	65	60	55	50
Aerosil	5	5	5	5	5	5	5	5	5	5	5	5
Sweetner	10	10	10	10	10	10	10	10	10	10	10	10
Banana flavour	1	1	1	1	1	1	1	1	1	1	1	1
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
Total (mg)	100	100	100	100	100	100	100	100	100	100	100	100

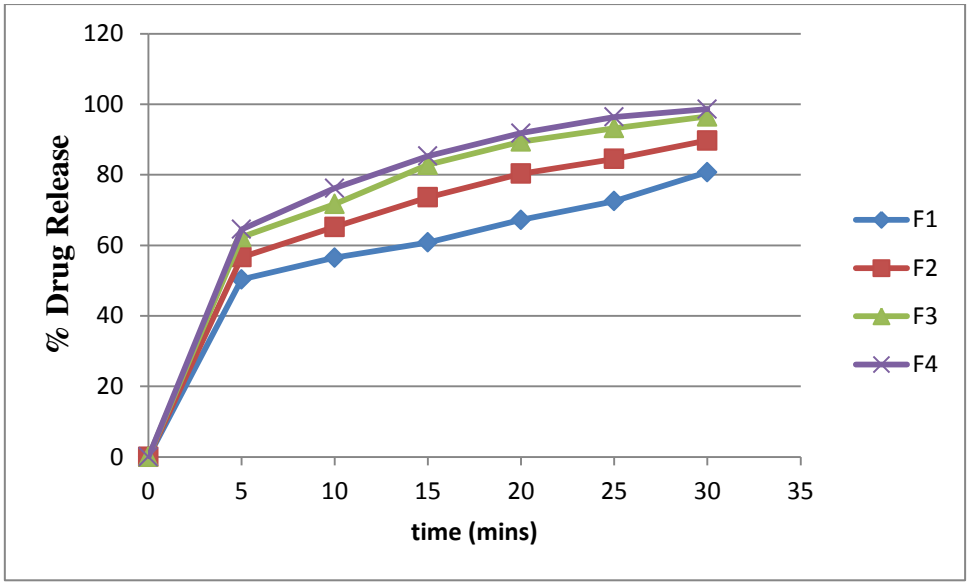

Fig 1: Cumulative % drug release Amlodipine besylate oral disintegrating tablets prepared with cross povidone.

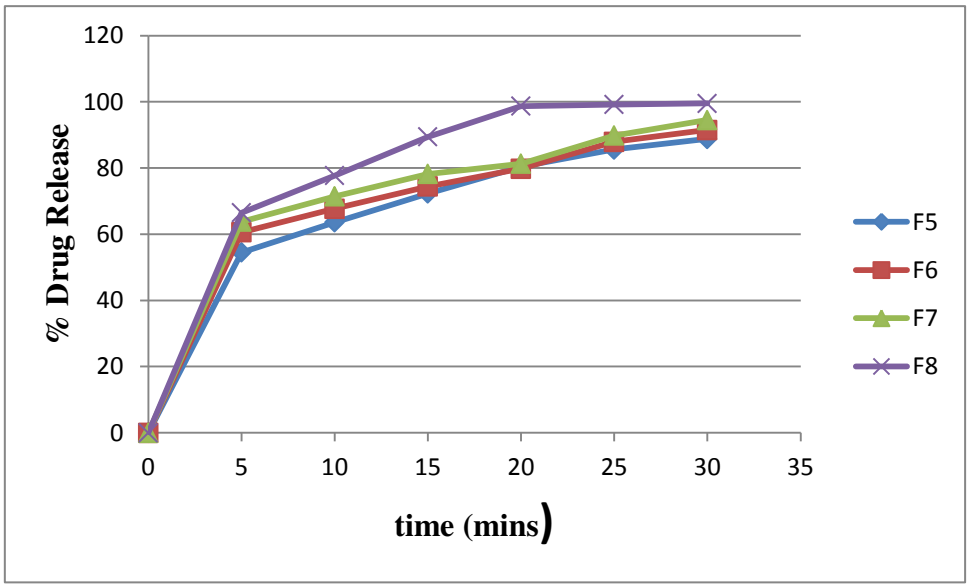

Fig 2: Cumulative % drug release Amlodipine besylate oral disintegrating tablets prepared with crosscarmellose.

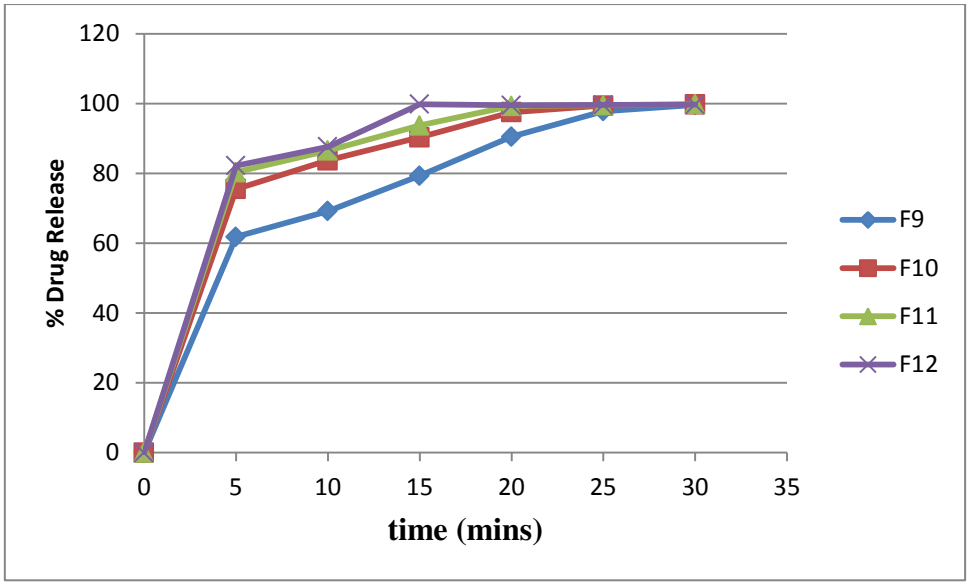

Fig 3: Cumulative % drug release Amlodipine besylate oral disintegrating tablets prepared with Sodium starch Glycolate.

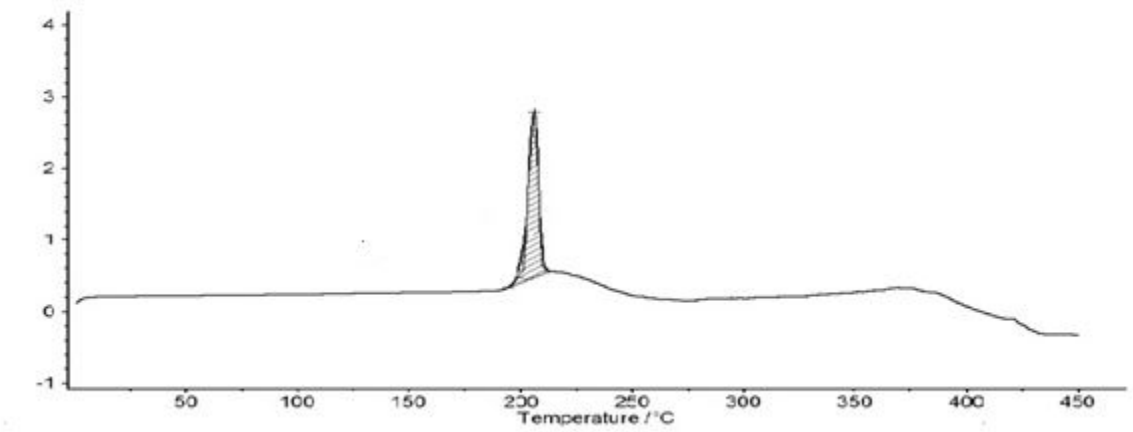

Fig 4: DSC thermogram of pure Amlodipine besylate

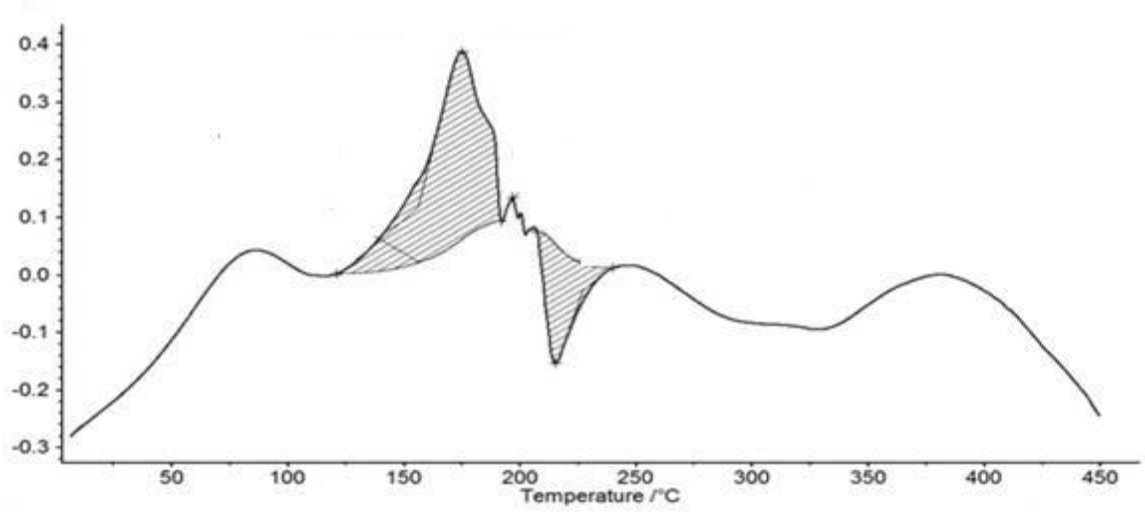

Fig 5: DSC thermogram of Amlodipine besylate oral disintegrating tablets.

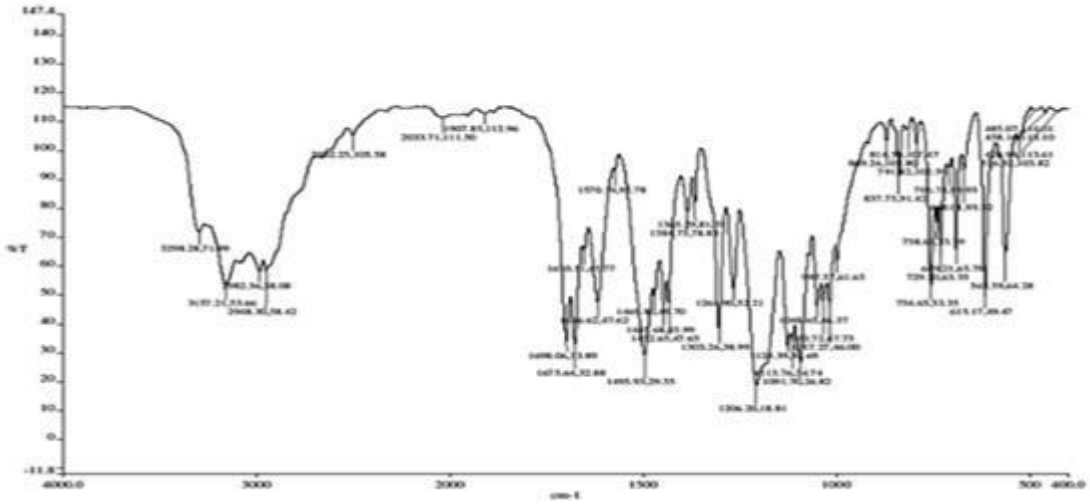

Fig 6: FTIR spectrum of Pure Amlodipine besylate

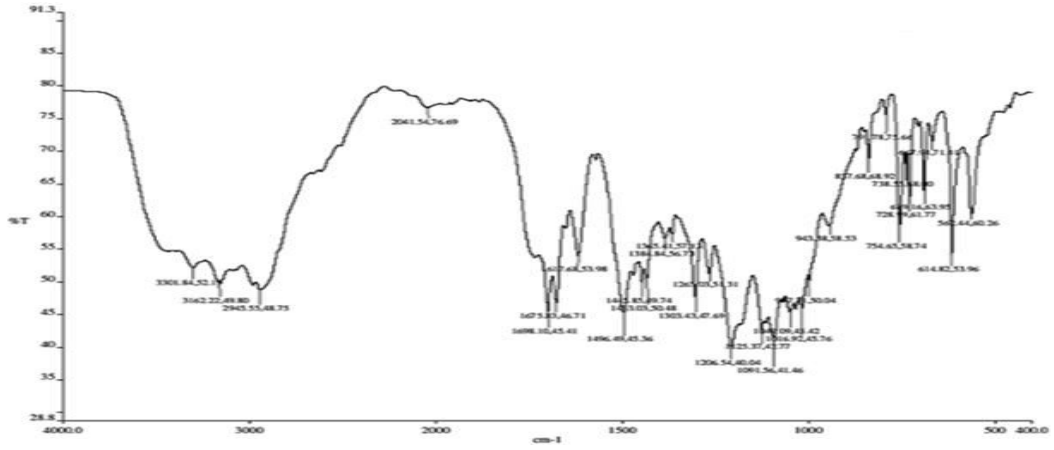

Fig 7: FTIR spectrum of Amlodipine besylate oral disintegrating tablets

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