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Formulation and evaluation of amlodipine besylate orally disintegrating films

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The objective of this study was to prepare the orally disintegrating films of Amlodipine besylate by solvent casting method using polymers such as HPMC E3, HPMC E6 and natural polymer Pullulan gum. The films were characterized for various physicochemical properties such as thickness measurement, weight variation, % drug content, folding endurance, *in vitro* disintegration time, *in vitro* dissolution. The formulation with Pullulan gum, F9 is found to be best formulations. In vivo taste and mouth evaluation were conducted on selected age group of the people having 30-35 years and it was found that the films prepared with Sweetener acesulfame potassium and orange flavor gives excellent taste and mouth feel. The DSC and FTIR study revealed no drug polymer interactions. SEM study showed that films were clear, transparent and had a smooth surface the surface property. The prepared orally disintegrating films have good commercial success.

Keyword: Amlodipine Besylate, HPMC, Hypertension, Oral disintegrating films, Pullulan gum.

1. Introduction

Fast dissolving films provides an elegant platform for systemic drug delivery of active pharmaceutical agents. Recent advancements in the formulation technology have presented variable dosage form alternatives from oral route for administering wide group of patients. Although buccal drug delivery has lately become an important route of drug administration, various bioadhesive mucosal dosage forms are being developed [1]. In the late 1970s, fast-dissolving drug delivery systems were first developed as an alternative to tablets, capsules, and syrups for paediatric and geriatric patients who were experiencing difficulties in swallowing oral dosage forms [2]. The oral fast disintegrating dosage forms is also known as fast dissolve, quick disintegration, rapid dissolve, and rapid melt. FDFs can be defined as, solid dosage form that disintegrates or dissolves quickly in the oral cavity, resulting in solution without the need of water [3]. After placing the film on the top of the tongue due to accessibility of larger surface area leads to quick disintegration and dissolution in the oral cavity within seconds by rapid wetting with saliva and gets absorbed directly and enters the systemic circulation without undergoing first-pass hepatic metabolism and thus increases the bioavailability [4, 5, 6].

Easy ingestion and swallowing, pain avoidance make the oral mucosa as a very attractive and selective site for systemic drug delivery. Due to the avoidance of first pass effect, fewer doses are required which can lead to reduction in side

effects associated with the active agent [7]. Advantages of films include more stability, durable and quicker release of drug than other conventional dosage forms; avoid first pass metabolism [8], pleasant mouth feel, accurate dosing, and rapid onset of action and no need of water with patient compliance, ease of handling and transportability [9]. Various categories of drugs such as antiemetic, analgesics, antiallergic, antiepileptic, anxiolytics, cardiovascular agents, hypnotics, diuretics, neuroleptics, sedatives and drugs used for erectile dysfunction, anti alzheimers, expectorants and antitussive can also be formulated as oral fast dissolving films [10-15].

The water-soluble polymers are most widely used in the formulation of fast dissolving films to achieve rapid disintegration, good mouth feel and required mechanical properties to the films. The disintegration rate of the polymers can be decreased by increasing the molecular weight of polymer film bases. Different viscosity grades of HPMC such as E3, E6 and natural polymer Pullulan gum was used in the present research work. Some of the water soluble polymers widely used as film former are HPMC E-3 and K-3, Methyl cellulose A-3, A- 6 and A-15, Pullulan gum [7, 16].

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. Bioavailability is 64-90% and absorption is not affected by food. Amlodipine is extensively (90%) is converted to inactive metabolites through hepatic metabolism by cytochrome P450 3A4 isozyme with 10% of the parent compound and 60% of the metabolites excreted in the urine [17, 18].

2. Materials and method

2.1. Materials

Amlodipine Besylate was obtained as gift sample from Aurobindo Pharma Labs. HPMC E3 and E6 grades were obtained from Colorcon Asia Pvt. Ltd. Pullulan gum was obtained from Shilex Chemicals. Dichloro methane, Poly ethylene glycol was obtained from S.D. Fine Chem Ltd. All other excipients were of fine grade and used as received.

2.2. Method

The ODF of Amlodipine Besylate were prepared using HPMC E3, HPMC E6 and Pullulan gum in the ratios of 1:1, 1:2.5, 1:5 and 1:7.5 drug to polymer ratio. The polymeric solution was prepared by using dichloromethane and methanol and kept aside about 5 to 6 hrs for swelling of polymer.

Table 1: Formulation development of Amlodipine Besylate Oral Disintegrating films

Ingredients	Formulation codes										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Amlodipine besylate (mg)	5	5	5	5	5	5	5	5	5	5	5
HPMC E3 (mg)	5	12.5	25	37.5	----	----	----	----	----	----	----
HPMC E6 (mg)	----	----	----	----	5	12.5	25	37.5	----	----	----
Pullulan gum (mg)	----	----	----	----	----	----	----	-----	12.5	25	37.5
Dichloromethane (ml)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Methanol (ml)	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
PEG 400	5	5	5	5	5	5	5	5	5	5	5
Acesulfame potassium (mg)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Orange flavor (mg)	1	1	1	1	1	1	1	1	1	1	1

Amlodipine Besylate was dissolved in measured quantity of solvents and this drug solution was added to the above polymeric solution. This step was followed by the addition of plasticizers such as PEG 400, sweetener and flavors. Uniformity of drug content is achieved by mixing in cyclo mixer for 15-20 minutes. The solution was cast on a prepared mould and air dried for 45 minutes. The film was carefully removed from the mould, checked for imperfections, and cut to the required size to deliver the equivalent dose (2×2 cm^2) per strip. Film samples with air bubbles, cuts, or imperfections were excluded from the study.

3. Evaluation of Films

3.1. Weight variation

The weights of the prepared films were determined by using electronic balance [19].

3.2. Thickness

The thickness of the batches was evaluated by using calibrated Vernier calipers. Thickness of the Film was measured at five positions i.e. central and the four corners and the mean thickness was calculated [20].

3.3. Folding endurance

The folding endurance was done manually for the prepared films. A strip of film was cut and folded repeatedly at the same place till it broke. The number of times the film could be folded at the same place without breaking is taken as the value of folding endurance [21].

3.4. Drug content

Out of 5 films one film was randomly selected, weighed and added to 100 ml of 0.01N HCl in a volumetric flask. The solution was sonicated for 30 mins. The solution was diluted suitably and absorbance of the resulted solution were measured using UV-Visible spectrophotometer against 0.01N HCl as blank at λ max 244 nm [20].

3.5. *In vitro* disintegration time

In vitro disintegration time of the films was determined visually in a petri glass dish with 25 ml 0.01N HCl and swirling was done at every 10 sec. the time when the film starts to break or disintegrates is taken as disintegration time [22].

3.6. *In-vitro* dissolution studies

In vitro drug release study was carried out in USP basket type (type I) apparatus using 0.01 N HCl acidic buffer as a dissolution medium. The temperature was maintained at 37±0.5 ^{0}C and at basket rotation with 50 RPM. 5 ml of aliquots were withdrawn at different time intervals and same amount of fresh prewarmed dissolution medium was replaced. The aliquots were assayed for drug content at λ max 244 using UV-spectrophotometer. The cumulative percentage drug release was calculated [23, 24, 25].

4. Drug excipient compatibility study

4.1. Fourier Transform Infrared spectroscopy (FT-IR) [26]

Drug excipient interaction studies were carried out by using BRUKER FT I.R. to confirm possible interactions between the drug and polymer. The film was finely ground with KBr to prepare the pellets under a hydraulic pressure of 600 psi and a spectrum was scanned in the wavelength range of 400 and 4000 cm^{-1}. The physical state of the drug in the formulation was characterized by using differential scanning calorimeter (DSC 60, Shimadzu). The analysis was performed by heating 10 mg of sample on aluminum crimp pans at a rate of 100 c/min in a nitrogen atmosphere (50 ml, min^{-1}).

4.2. Differential scanning colorimetric study (DSC) [27]

Thermal properties of pure drug and the formulation 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 10 k/min were applied with a nitrogen purge of 60 ml/min over a temperature range of 0 to 450 ^{0}C. An aluminium pan was used as a reference. A quality equivalent to 2 mg of pure drug was used for the study.

4.3. Scanning electron microscopy (SEM) [28]

The surface morphology of the optimized formulations was observed with scanning electron microscope. The samples were attached to the slab surfaces with double-sided adhesive tapes and the scanning electron photomicrograph was taken at 200X, 500X and 1000X magnification.

5. Results and Discussion

Amlodipine Besylate oral disintegrating films were prepared using HPMC E3, E6 and pullan gum as film forming polymer and PEG 400 as the plasticizer. The formed films were evaluated for various properties like weight variation, folding endurance, thickness, drug content etc. The results showed that all the films have a smooth surface texture. Films were not formed in the formulation F1 and F5 due to low polymer concentration. The weight variations of the films were found to be uniform in all the batches. The thickness of the films was found to be in the range of 0.08 mm to 0.3 mm. Films were having adequate thickness for handling and use. The folding endurance was found to be above 300 indicating that the plasticizer concentration was adequate. % Drug content uniformity evaluation results were in between 97.6±1.3 to 99.8±1.2, thus the films were uniform and drug was uniformly distributed in the films. The disintegration time of the films was evaluated using 0.01 N HCl buffer. The disintegration time of films in formulations F2 to F4 was in the range of 23 sec to 40 sec, in F6 to F8 it was in the range of 29 sec to 50 sec, in F9 to F11 it was in the range of 18 sec to 37 sec. It was observed that the disintegrating time was increased as the concentration of polymer was increased. Formulations F2 and F9 disintegrated most rapidly.

5.1. *In vitro* drug release study Amlodipine Besylate oral disintegrating films

In vitro drug release of the oral disintegrating films prepared with HPMC E3, was faster at initial 5 minutes and found to be 89% for F-2 formulation and the dissolution rate were slower as the polymer concentration was increased. However all the formulations released 99% within 20 mins. *In vitro* drug release of the oral disintegrating films prepared with HPMC E6, the formulation F4 showed complete drug release in 15 mins. Formulation F5 and F6 showed complete drug release in 20 mins. *In vitro* drug release of the films prepared with pullulan gum, the formulation F9 showed 95% of drug release in 5 mins and complete drug release within in 10 mins. F10 and F11 extended the drug release upto 20 mins.

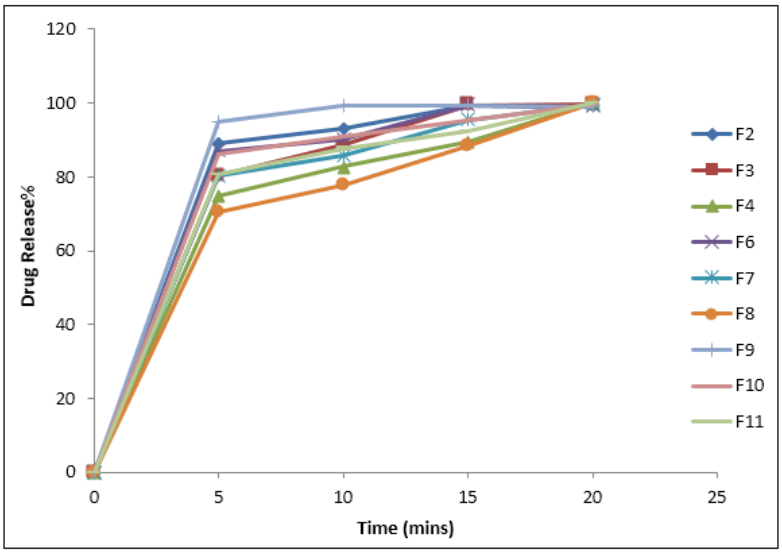

Fig 1: Cumulative % drug release vs time profile of Amlodipine Besylate ODF prepared with different ratios of Polymer HPMC E3, E6 and Pullulan gum.

Table 2: *In vivo* taste and mouth feel evaluation of the Amlodipine Besylate orally disintegrating film:

S. No	F2(B)	F2(O)	F6(B)	F6(O)	F9(B)	F9(O)	F2(B)	F2(O)	F6(B)	F6(O)	F9(B)	F9(O)
	Taste						Mouth feel					
1	+	+++	+	+++	+	+++	+	+++	+	+++	+	+++
2	+	+++	+	++	+	+++	+	+++	+	++	+	+++
3	+	+++	+	+++	+	+++	+	+++	+	++	+	+++
4	+	+++	+	+++	+	++	+	++	+	+++	+	+++
5	+	+++	+	++	+	+++	+	+++	+	+++	+	+++
6	+	+++	+	+++	+	+++	+	+++	+	+++	+	+++
7	+	++	+	+++	+	+++	+	+++	+	+++	+	+++
8	+	+++	+	+++	+	+++	+	+++	+	+++	+	+++
9	+	+++	+	+++	+	+++	+	+++	+	+++	+	+++
10	+	+++	+	+++	+	+++	+	+++	+	+++	+	++
11	+	++	+	+++	+	+++	+	+++	+	+++	+	+++
12	+	+++	+	+++	+	++	+	+++	+	+++	+	+++
13	+	+++	+	+++	+	+++	+	++	+	++	+	+++
14	+	+++	+	+++	+	+++	+	+++	+	+++	+	+++
15	+	+++	+	+++	+	+++	+	+++	+	+++	+	+++
Excellent - +++, Moderate - ++, Good - +												

For taste evaluation the films were prepared with sweetening agent such as acesulfame potassium and aspartame and for flavor evaluation films were prepared with orange, banana flavor .The prepared films were cut into 2.0 X 2.0 cms In vivo taste and mouth evaluation were conducted on selected age group of the people having 30-35 years 15 healthy male volunteers as per the permission approved from human ethical committee. It was found that the film prepared with polymer HPMC E3 and containing Sweetener acesulfame potassium and orange flavor has an excellent taste and mouth feel than the film containing aspartame Sweetener and banana flavor.

6. Drug and excipient compatibility

6.1. Differential Scanning Calorimetric (DSC) study

Selected formulations of Amlodipine Besylate films were characterized for DSC. The pure Amlodipine Besylate showed a sharp exothermic peak at 206.0 ^{0}C. Similar exothermic peaks were observed at similar temperature in the prepared films at 198.8 ^{0}C for HPMC E3, 196.4 ^{0}C for HPMC E6 and 185.0 ^{0}C for Pullulan gum. The literature of Amlodipine Besylate shows the DSC peaks in between 170-207 ^{0}C. This indicates that the no interaction between drug and selected polymers.

6.2. Fourier Transform Infrared Spectroscopy (FT-IR) study

The physicochemical compatibility of the drugs and polymers was established through FTIR studies. FTIR study was conducted on the selected formulations prepared with combination of different polymers such as HPMC E3, HPMC E6 and Pullulan gum. The spectrum peak points of the formulation were similar with that of the pure Amlodipine Besylate clearly indicating that there is no drug-polymer interaction.

6.3. Scanning Electron Microscopy (SEM) study

SEM determines the surface morphology of the film as they revealed as best formulation. The surface morphology of the optimized formulations was observed with scanning electron microscope. The samples were attached to the slab surfaces with double-sided adhesive tapes and the scanning electron photomicrograph was taken at 200X, 500X and 1000X magnification.

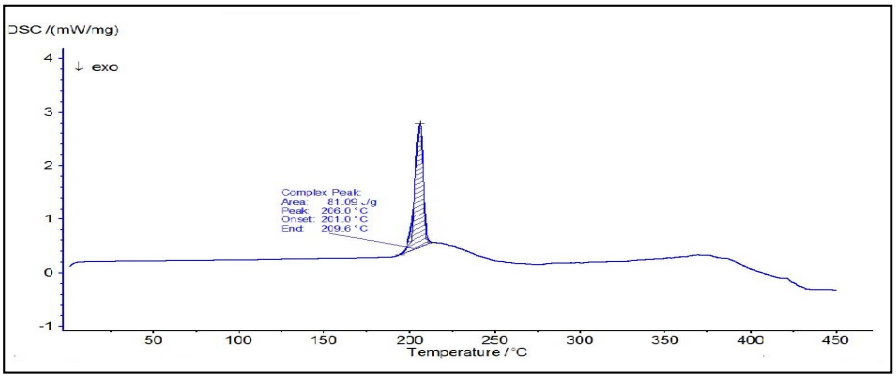

Fig 2: DSC thermograph of the pure Amlodipine Besylate

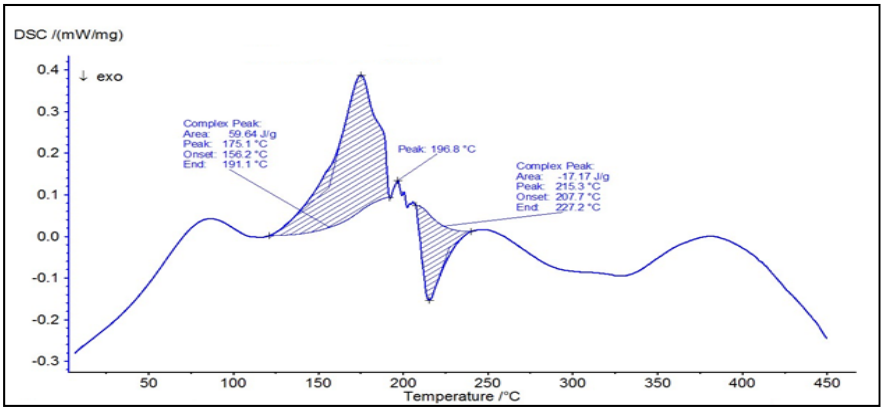

Fig 3: DSC thermograph of the Amlodipine besylate ODFs prepared using HPMC E3

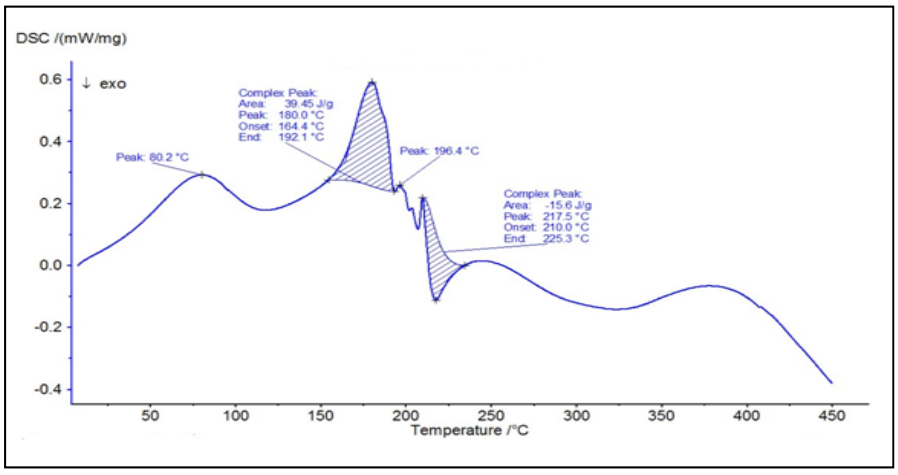

Fig 4: DSC thermograph of the Amlodipine Besylate ODFs prepared using HPMC E6

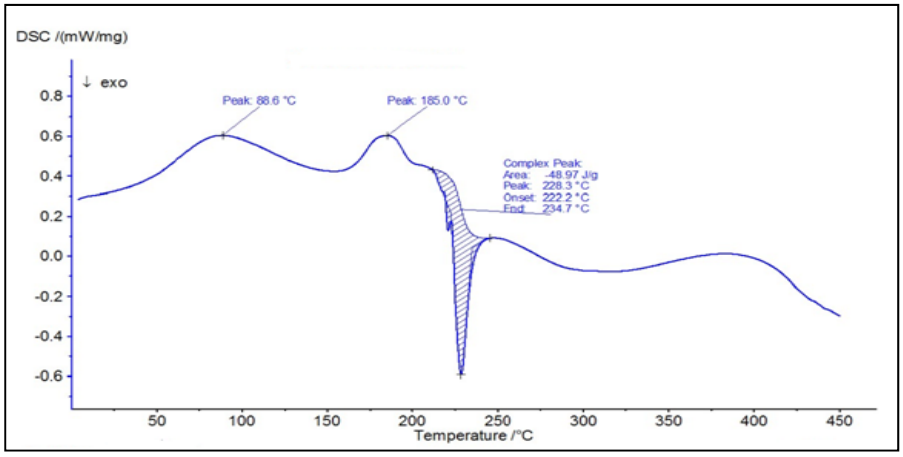

Fig 5: DSC thermograph of the Amlodipine Besylate ODFs prepared using Pullulan gum

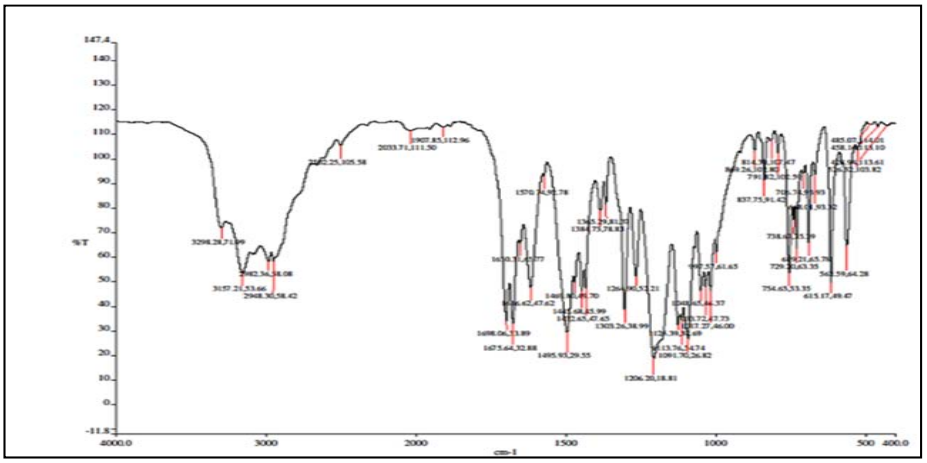

Fig 6: FTIR spectra of Pure Amlodipine Besylate

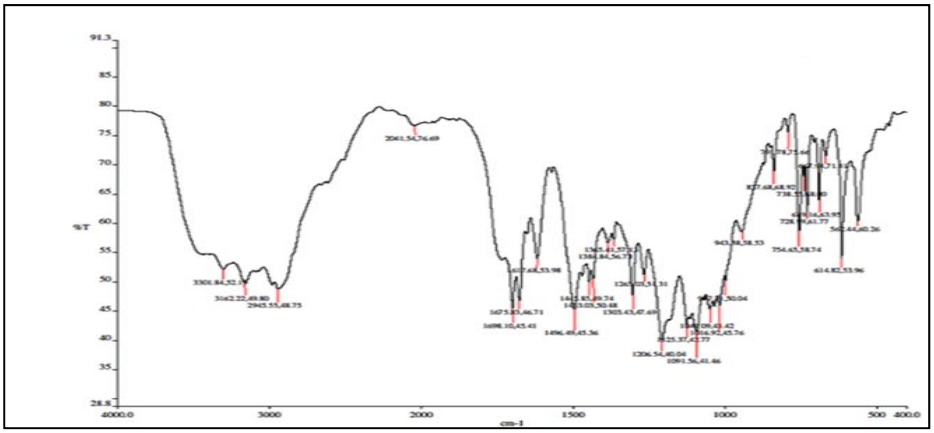

Fig 7: FTIR spectra of Amlodipine Besylate ODFs prepared using HPMC E3

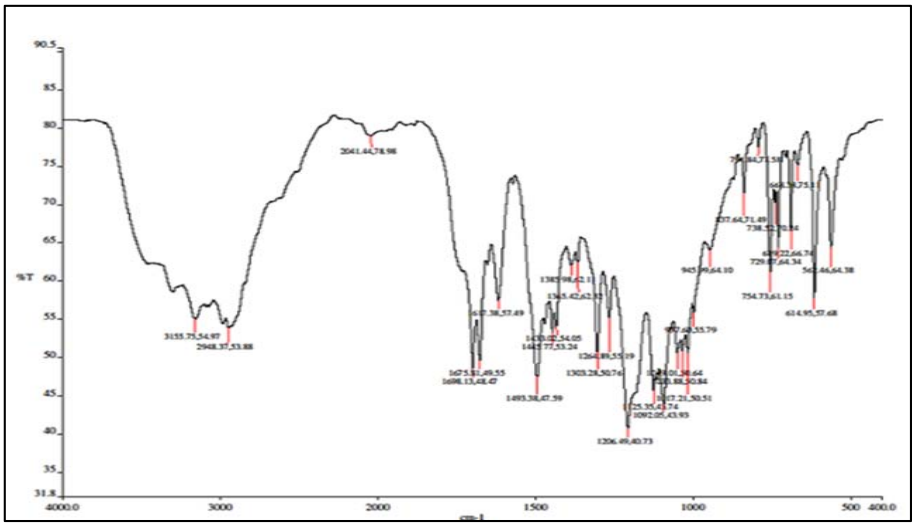

Fig 8: FTIR spectra of Amlodipine Besylate ODFs prepared using HPMC E6

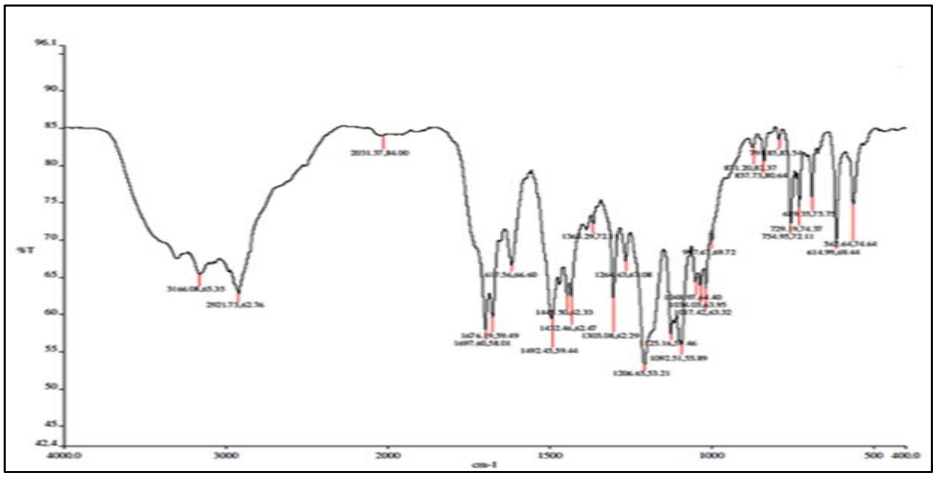

Fig 9: FTIR spectra of Amlodipine Besylate ODFs prepared using Pullulan gum

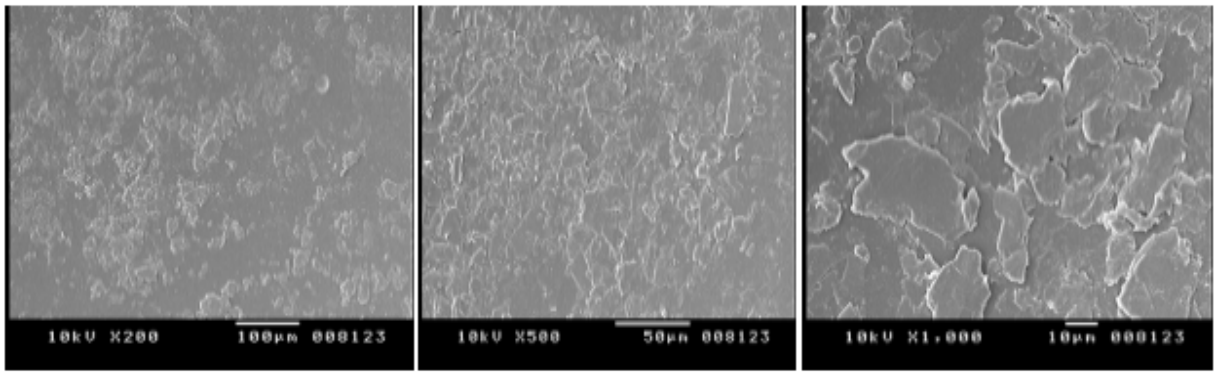

Fig 10: SEM images of film containing Amlodipine Besylate prepared with HPMC E3

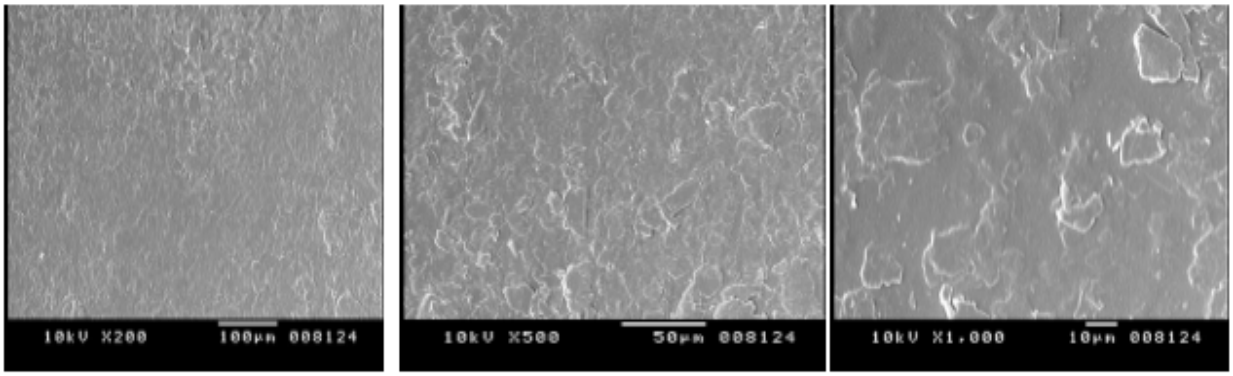

Fig 11: SEM images of film containing Amlodipine Besylate prepared with HPMC E6

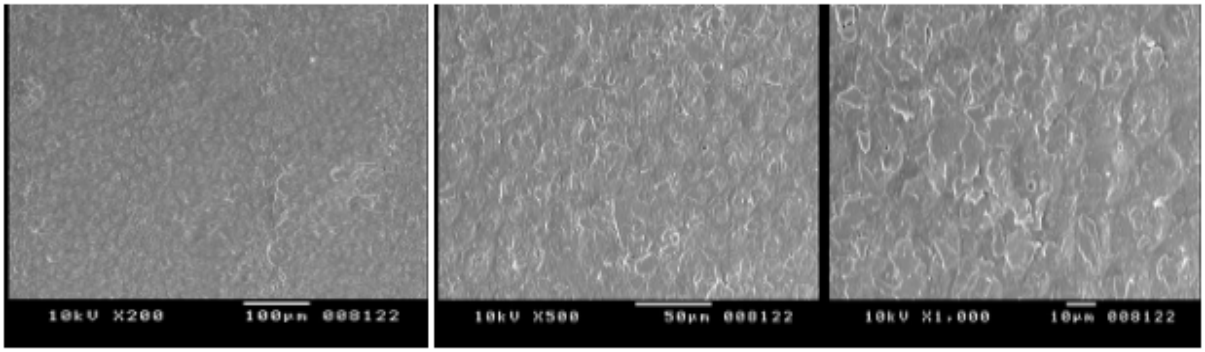

Fig 12: SEM images of film containing Amlodipine Besylate prepared with Pullulan gum

7. Conclusion

In this study, Amlodipine Besylate oral disintegrating films were prepared using polymer HPMC E3, E6 grades and Pullulan gum by solvent casting method. It was observed that concentration of polymer effects the formation of film and dissolution time of the formulations. The quality control tests results were within the acceptable limits. In this study best formulation was chosen from each polymer based on release parameters. F9 formulation is considered as the best according to the obtained results with disintegrating time of 18 sec and complete drug release in 10 mins. FTIR and DSC study indicated that there is no interaction between the drug and excipients.

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