Modern Applications of Bioequivalence & Bioavailability (MABB)

Juniper Publishers key to the Researchers

Review Article
Volume 1 Issue 3 - June 2017
DOI: 10.19080/MABB.2017.01.555570

Mod Appl Bioequiv Availab

The Effect of Different Polymers on the Drug Release Behavior from Fast Dissolving Amlodipine Besylate Oral Films for the Treatment of Hypertension

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Submission: June 22, 2017; **Published:** June 29, 2017

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Introduction

The antihypertensive effects of Calcium channel blockers (CCBS) have been used from decades [1]. Unlike BCS Class II drugs, Amlodipine is highly soluble Class III drug [2]. It is a second generation long acting dihydro calcium channel blocker used in the management of hypertension and angina pectoris. The initial dose is 5 mg dailyfor the management of hypertension. After the oral administration, it is well absorbed with a peak blood concentration of 6-12 hours having an elimination half-life of 30-50 hours [3,4].

Oral mucosal region is highly vascularized and it gives rapid absorption of drugs than oral route [5]. Drugs that are absorbed through the buccal mucosa and sublingual route directly enter the systemic circulation bypassing the first-pass metabolism in the liver [6,7]. Orally fast-dissolving film is new drug delivery system for the oral delivery of the drugs. It can be placed on the tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application [8]. The aim of the study was to design, develop and evaluate rapidly dissolving oral films of Amlodipine besylate. The objective of the study is to develop an oral film for the immediate release of drug and to evaluate the effect of different polymers with disintegrates on the fabrication of the film and drug release from the film.

Experimental

Materials

Amlodipine was obtained as a gift sample from Microlabs, Bangalore. HPMC and SSG procured from LobaChemie Pvt. Ltd, Mumbai. PVA, sodium alginate, glycerin and propylene glycol from SD fine chemicals, Mumbai. PVP was purchased from SISCO Research Laboratories. All the other chemicals used were of analytical grade.

Methods

A. Formulation of Amlodipine fast dissolving oral film: Fast dissolving oral films of amlodipine was formulated using solvent casting method. The polymer HPMC (2%, 2.5% and 3%), PVA and PVP (2%,2.5% and 3%) and Sodium alginate and SSG (1.5%, 2% and 2.5%) is dissolved in water and then the specified quantity of drug as well as plasticizers, other excipients were added and was air dried for 24 hours in petridishes.

B. Preparation of oral films using HPMC: HPMC (2%, 2.5% and 3%) were dissolved in water. Specified amount of drug and 20%w/w of plasticizers (glycerine, propylene glycol) were added to it. The above solution was poured onto a petridish and dried at room temperature. After 24 hours the dried films were taken out.

C. Preparation of oral films using PVA and PVP: PVA in percentage of 2%,2.5% and 3% were dissolved in water. 1% and 2% PVP were added as disintegrates to each of the polymer solutions. Then 55mg of drug and 20% of plasticizers (glycerine, propylene glycol) were added to it. The above solution was poured onto the petridish and dried in oven at a temperature of 60 ºC. After 24 hours the dried films were taken out.

D. Preparation of oral films using Sodium alginate and SSG: Sodium alginate in percentage of 1.5%, 2% and 2.5% were dissolved in water. Then 1% and 2% SSG was added to each of the polymer solution. Then 55mg of drug and 20%w/w of plasticizers (glycerine, propylene gycol) were added to it. The above solution was subjected to magnetic stirrer and was poured onto the petridish and was dried in room temperature and after 24 hours the dried films were taken out.

Results and Discussion

The calibration curve of Amlodipine in Phosphate buffer pH6.8 at 238nm (Figure 1) was carried out and R^2 was found to be 0.996.

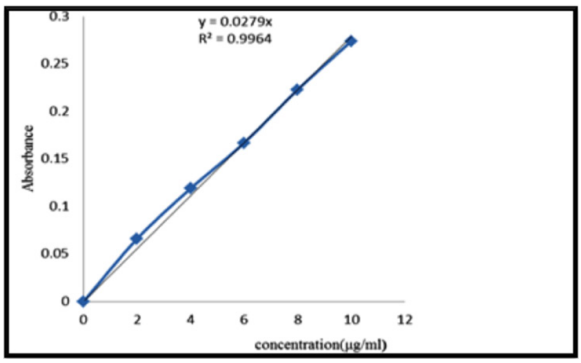

Figure 1: Calibration curve of Amlodipine in Phosphate buffer pH 6.8 at 238nm.

Fast dissolving oral films were prepared by solvent casting method using polymers such as hydroxyl propyl methylcellulose, polyvinyl alcohol and sodium alginate using poly vinyl pyrrolidone and sodium starch glycolate as disintegrates.

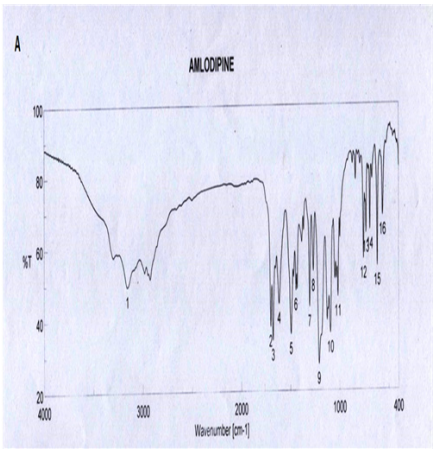

Figure 2: A. FT-IR spectra of Amlodipine (A) FT-IR spectra of formulation (A).

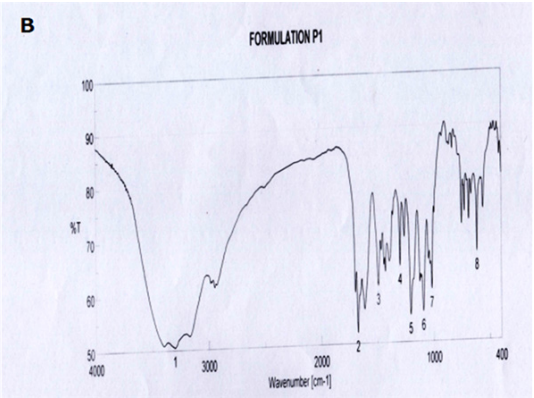

Figure 2: B. FT-IR spectra of Amlodipine (A) FT-IR spectra of formulation (B).

The FT-IR spectrum of the standard was analyzed and then superimposed with the samples to find out possible interactions between the drug and the polymers. All the characteristic peaks of Amlodipine were also found in the spectrum formulations Figure 2A & 2B. The results suggested that the drug is intact in the formulations and there was no interaction found between the drug and the excipients also the peaks in formulation showed slight variation due to the drug incorporation.

Table 1: Characteristic peaks of Amlodipine.

Sl. No	Wavelength (cm^{-1})	Specification
1	3158	Secondary -NH stretching
2	1092	C-Cl stretching
3	1698	C=O stretching of ester
4	1570	NH bending vibration
5	2926	CH_3-CH stretching

Table 2: Folding endurance of prepared HPMC, PVA and Sodium alginate films.

Formulation Code	Folding Endurance	Formulation Code	Folding Endurance	Formulation Code	Folding Endurance
H1	102	P1	128	S1	118
H2	115	P2	132	S2	108
H3	109	P3	140	S3	115
H4	105	P4	130	S4	120
H5	110	P5	137	S5	134
H6	116	P6	146	S6	126

Table 3: Thickness of prepared HPMC, PVA and Sodium alginate films.

Formulation Code	Thickness (mm)	Formulation Code	Thickness (mm)	Formulation Code	Thickness (mm)
H1	0.21	P1	0.15	S1	0.23
H2	0.23	P2	0.17	S2	0.25
H3	0.25	P3	0.2	S3	0.28
H4	0.2	P4	0.16	S4	0.25
H5	0.25	P5	0.19	S5	0.27
H6	0.28	P6	0.22	S6	0.29

Table 4: Weight of prepared HPMC, PVA and sodium alginate films.

Formulation Code	Weight of the Film (mg)	Formulation Code	Weight of the Film (mg)	Formulation Code	Weight of the Film (mg)
H1	36	P1	50	S1	46
H2	40	P2	58	S2	51
H3	54	P3	62	S3	58
H4	40	P4	54	S4	51
H5	45	P5	60	S5	56
H6	56	P6	64	S6	61

The physical evaluations and *in-vitro* drug release studies were performed for all the 18 formulations. The results are acceptable for folding endurance, thickness,weight uniformity,

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percentage moisture absorption, disintegration time, drug content and *in-vitro* drug release shown in Table 1-5. The surface pH results of the film was found to be nearly neutral and suitable for oral use as shown in Table 6. Films were analyzed for its drug content and all the formulations showed a satisfactory drug content values ranging from 60-93% which is in accordance with the standard values prescribed for drug content analysis shown in Table 7.

Table 5: Percentage moisture absorption of HPMC, PVA and Sodium alginate films.

Formulation Code	% Moisture Absorption	Formulation Code	% Moisture Absorption	Formulation Code	% Moisture Absorption
H1	2.54	P1	2.83	S1	6.36
H2	4.77	P2	5.36	S2	9.65
H3	5.82	P3	9.41	S3	12.74
H4	3.15	P4	3.5	S4	7.48
H5	3.21	P5	6.53	S5	13.72
H6	4.97	P6	8.61	S6	12.78

Table 6: Surface pH of prepared films of HPMC, PVA and sodium alginate.

Formulation Code	Surface pH	Formulation Code	Surface pH	Formulation Code	Surface pH
H1	6.54	P1	6.76	S1	6.67
H2	6.65	P1	6.63	S2	6.84
H3	6.69	P3	6.57	S3	6.55
H4	6.64	P4	6.68	S4	6.71
H5	6.57	P5	6.83	S5	6.73
H6	6.62	P6	6.75	S6	6.6

Table 7: Assay of prepared HPMC, PVA and Sodium alginate films

Formulation Code	Assay (%)	Formulation Code	Assay (%)	Formulation Code	Assay (%)
H1	96.35	P1	97.67	S1	96.82
H2	95.65	P2	95.12	S2	93.15
H3	93.84	P3	92.03	S3	91.34
H4	95.74	P4	96.81	S4	94.06
H5	92.87	P5	94.69	S5	92.26
H6	91.96	P6	90.18	S6	90.72

Table 8: Disintegration time of prepared HPMC, PVA and Sodium alginate films.

Formulation Code	Disintegration Time(sec)	Formulation Code	Disintegration Time(sec)	Formulation Code	Disintegration Time(sec)
H1	20	P1	15	S1	42
H2	25	P2	23	S2	60
H3	40	P3	30	S3	80
H4	24	P4	17	S4	44
H5	31	P5	26	S5	57
H6	38	P6	35	S6	80

Table 9: Dissolution study for HPMC films.

Time (min)	Cumulative Percentage Drug Release					
	H1	H2	H3	H4	H5	H6
2	42.92	37.12	22.57	43.7	26.84	20.85
4	51.56	43.74	37.89	54.78	41.56	39.17
6	61.36	58.34	45.25	62.83	47.49	44.32
8	72.68	65.1	52.54	70.54	58.76	51.61
10	85.64	76.34	68.18	81.32	64.52	62.97
15	90.56	83.87	75.45	90.93	74.06	73.1
20	93.34	90.97	79.28	92.91	86.11	80.15
25	93.32	93.45	90.64	93.92	92.12	87.84
30	93.33	93.42	90.63	93.93	92.15	90.19

Table 10: Dissolution study for PVA films.

Time (min)	Cumulative Percentage Drug Release					
	P1	P2	P3	P4	P5	P6
2	44.86	41.6	38.95	35.1	33.84	27.46
4	50.15	49.93	45.72	45.78	40.5	35.17
6	61.05	55.62	54.78	57.72	49.95	44.3
8	74.75	66.15	65.11	65.14	58.76	50.78
10	83.76	75.07	70.76	77.55	64.52	63.02
15	93.88	86.91	81.05	81.62	78.86	75.87
20	93.87	92.76	91.67	92.41	85.12	81.15
25	93.85	92.75	91.66	92.42	91.73	87.84
30	93.86	92.76	91.68	92.4	91.76	91.52

Table 11: Dissolution study for Sodium alginate films.

Time (min)	Cumulative Percentage Drug Release					
	S1	S2	S3	S4	S5	S6
2	40.42	38.85	36.57	37.58	37.01	36.54
4	46.66	44.73	41.58	44.29	43.58	41.93
6	54.87	52.81	49.97	53.11	52.67	50.96
8	65.06	63.9	57.85	62.74	61.75	59.87
10	75.13	74.36	68.12	70.58	69.92	67.72
15	86.54	84.65	72.37	81.85	78.75	75.3
20	91.72	91.67	85.06	91.52	91.04	82.46
25	91.74	91.68	91.42	91.53	91.03	90.94
30	91.73	91.66	91.43	91.53	91.05	90.95

The formulation P1 (2 %PVA and 2%SSG) was found to have the maximum disintegration time of 15 min. The *in-vitro* release studies of formulation P1 showed maximum release of 93.86% within 30 minutes, which shows that the increase in polymer concentration decreases the drug release shown in Table 8-11. The kinetic data suggest that the formulation fit into 1st order equation for release of drug from the homogenous film and the release mechanism was found to be fickian diffusion. The stability studies showed that there was not much change in the physical appearance, drug content and dissolution When the oral film preparation was stored in a chamber controlled at 40 °C and 75% in humidity for 1 to 3 months, no apparent changes in the

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drug content, form or color of preparations were observed in Table 12. The drug content were was stable ranging from 97.67% to 93.96% during the study after storage at 40 °C and 75% humidity (accelerated condition). Therefore, the formulated Amlodipine fast dissolving oral film using the combination of PVA and SSG would be a promising alternative for safer and effective treatment of hypertension.

Table 12: Stability studies of formulation P1.

Condition: 40 ºC±2 ºC/75% RH±5% RH										
Parameters observed for formulation P1										
Sl no:	Formulation	Physical appearance			Drug content			Dissolution		
		Initial	1st Month	3rd Month	Initial	1st Month	3rd Month	Initial	1st Month	3rd Month
1	P1	No change	No change	No change	97.67	96.54	95.96	93.88	93.61	92.67

Conclusion

A fast dissolving oral film of Amlodipine Besylate by solvent casting method was successful. Polymers such as HPMC, PVA and sodium alginate along with disintegrate like Poly Vinyl Pyrrolidone (PVP) and Sodium Starch Glycolate (SSG) were used. All physic-chemical studies of the prepared films are comparable within the range. The formulation P1 (2 %PVA and 2%SSG) with maximum release rate was found to be the best formulation among the 18 formulations. Future studies using animal models will provide more effectiveness of the films *in-vivo*.

Acknowledgement

The authors are likely to express sincere thanks to KMCH College of Pharmacy, Kalappatty Road, Coimbatore, TN for providing the necessary facilities to carry out the research.

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