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Design and Characterization of Bilayered Buccal Tablets of an Anticonvulsant Drug.

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ABSTRACT

The aim of the present research work is to develop bilayered buccal tablets of an anticonvulsant drug midazolam. Bilayered buccal tablets were prepared by wet granulation method employing different types and levels of polymers viz. sodium alginate, ethyl cellulose, HPMC K15M, cabopol 940P. The granules were evaluated for angle of repose, density and compressibility index, which showed satisfactory results. The bilayer tablet contains an immediate release layer containing the drug along with super disintegrant sodium starch glycolate. The tablet also has a sustained release layer prepared using different polymers like HPMC K15M, ethyl cellulose and carbopol 940P in different ratios with the drug. The immediate and sustained release layers were compressed into bilayer tablets by double compression. Compressed tablets were evaluated for thickness, friability, hardness, uniformity of weight, content of active ingredient, swelling index and *in vitro* dissolution studies. FT-IR spectra revealed that there were no interactions between drug and polymers. All the formulation showed compliance with pharmacopoeial standards. It was observed that bilayer buccal tablet prepared using HPMC K15M in 1:3 ratio exhibited the best release profile and able to sustain the drug release for 7 h. The selected formulations were subjected to stability studies at different temperature and humidity conditions as per ICH guidelines. The drug release data followed zero order kinetics and the release data were further fitted to various mathematical models such as Higuchi, Korsmeyer-Peppas to evaluate the mechanism of the drug release which was found to be by non-Fickian diffusion.

Keywords: Midazolam, FT-IR, Wet granulation, Kinetics

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INTRODUCTION

For many active drugs to be administered systemically, the oral route has been the preferred route of administration. When administered by the oral route, however, many therapeutic agents have been reportedly subjected to extensive pre-systemic elimination by gastrointestinal degradation or hepatic metabolism. Results of low systemic bioavailability, short duration of therapeutic activity and formation of inactive or toxic metabolites have been often reported [1] .In recent years, the interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs. Drug delivery via the buccal route, using bioadhesive dosage forms offers such a novel route of drug administration [2]. Buccal delivery involves administration of desired drug through the mucosal membrane lining of oral cavity. The mucosal lining of oral cavity offers some distinct advantages. It is richly vascularized and easily accessible for the administration and removal of a dosage form. Additionally, buccal drug delivery has high patient acceptability compared to other non-oral routes of drug administration. Extensive first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via buccal route [3]. The thin mucin film, which exists on the surface of the oral mucosa, may provide an opportunity to retain a drug delivery system in contact with the mucosa for prolonged periods if it is designed to be mucoadhesive. Such system ensures a close contact with absorbing membrane, thus optimizing the drug concentration gradient across the biological membrane and reducing the differential pathway. Therefore, the oral mucosa may be a potential site for controlled or sustained drug delivery. In this respect, the buccal and gingival areas are associated with a smaller flow of saliva, as compared to the sublingual region. Thus the duration of adhesion of the delivery system would be longer at these areas than at the sublingual region [4].

MATERIALS AND METHODS

Reagents and chemicals

Midazolam was obtained as a gift from Yarrow Chemicals Ltd. (Hyderabad, India); HPMC K15M and Carbopol were obtained from Lobie Chemicals Ltd. (Mumbai, India);

Mixed Standard Preparation

The standard stock solution was prepared as per the method described in methodology section and scanned by UV Spectrophotometer as per methodology section. The UV absorption spectrum of Midazolam showed peak at 219nm against phosphate buffer pH 6.8 used as blank and the same was used for further analysis.

FT-IR study

The successful formulation of a stable and effective solid dosage form depends on the careful selection of the polymer that is added to facilitate administration, promote the consistent release, improved bioavailability and protects from degradation. FTIR can be used to investigate and predict any physicochemical interactions between components in a

formulation and can therefore be applied to the selection of suitable chemically compatible polymer.

Preparation Bilayer Buccal Tablets of Midazolam

Preparation of granules for immediate release layer and sustained release layer

Accurately weighed quantity of drug (midazolam), and other ingredients are added together and mixed. The fast release granules are prepared by wet granulation technique by blending midazolam uniformly with sodium starch glycolate using starch paste (10% w/w) as binder as per the formulae given in the table 1 .The cohesive mass obtained was passed through 1000µm sieve, dried in a hot air oven for 1 hour at 60^0C. The dried granules were again passed through a 1000µm sieve to break the agglomerates. The granules were mixed with talc and magnesium stearate for 15 minutes. The resulting granules were ready for compression and for sustained release layer same above procedure will be done whereas instead of starch paste we use PVP paste (10% w/w) and the resulting granules were ready for compression.

Table 1: Composition of immediate release layer of Midazolam

Sl. No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Midazolam	5	5	5	5	5	5	5	5	5
2	Sodium starch glycolate	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
3	Lactose	20	20	20	20	20	20	20	20	20
4	Micro crystalline cellulose	9	9	9	9	9	9	9	9	9
5	Starch paste	4	4	4	4	4	4	4	4	4
6	Magnesium stearate	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
7	Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Physicochemical Evaluation of Bilayer buccal Tablets

***In vitro* drug release studies**

These studies were carried out using a USP XXIV type II dissolution apparatus. The tablet was fixed with a cyanoacrylate adhesive to a glass plate and placed at the bottom of the vessel containing phosphate buffer of pH 6.8 in each flask. The samples were withdrawn, filtered and measured at 219 nm with a UV visible spectrophotometer.

The medium used was 900ml. Tablets equivalent to 14.5 mg of the pure drug were used. The tests were carried out for 6hrs and at 50 rpm at 37° ± 0.5 °C. 5ml of the aliquots were withdrawn at different predetermined time intervals and filtered. The

required dilutions were made with dissolution medium and the solution was analysed for the drug content spectrophotometrically at 219nm against suitable blank.

RESULTS AND DISCUSSION

The fomulations followed Korsemeyer Peppas model characteristics. It was found from the Korsemeyer-Peppas equation that the F3 formulation followed anomalous transport. Among the 3 formulations prepared using HPMC, ethyl cellulose and carbopol polymers, F3 prepared using HPMC has shown better drug release at the end of 7 hours i.e.98.15%. The relative complexity of the prepared formulation may indicate that the drug release was controlled by more than one process; a coupling of diffusion and erosion.

The data of formulation F3 was plotted as time vs amount of drug remained and the plot was found to be linear showing that the drug release followed the zero order rate kinetics. Formulation F3 containing HPMC K15M in the ratio 1:3 gave sustained release profile comparatively better than the other formulations. In present study, stability studies were carried out at 25 ± 2^0C / 60% RH and 40± 2^0C / 75% RH for the following selected formulations for 60 days and were found stable [5-9].

Table 2: Composition of sustained release layer of Midazolam

Sl. No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Midazolam	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5
2	HPMC K 15 M	9.5	19	28	--	--	--	--	--	--
3	Ethyl cellulose	--	--	--	9.5	19	28	--	--	--
4	Carbopol 940P	--	--	--	--	--	--	9.5	19	28
5	Sodium Alginate	15	7	4	12	5	4	9.5	19	28
6	Aspartame	2	2	2	2	2	2	2	2	2
7	Citric Acid	7	5	2.5	5	5	2.5	5	8	5
8	Mannitol	31	26	26	26	23	23	26	26	15
9	Lactose	30	35	35	40	43	35	35	35	15
10	PVP paste	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
11	Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
12	Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

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Table 3: Physico Chemical Evaluations of Formulations

Formulations	PARAMETERS				
	Angle of Repose (θ)*	Bulk Density (g/ml)*	Tappped Density (g/ml)*	Carr's Index (%)*	Hausner Ratio*
F1	29.5 ± 0.28	0.49±0.03	0.56±0.02	12.50±0.11	1.14±0.03
F2	26.0±0.15	0.53±0.04	0.61±0.01	13.11±0.13	1.15±0.04
F3	25.5±0.35	0.46±0.05	0.53±0.03	13.21±0.13	1.15±0.03
F4	29.27±0.53	0.55±0.04	0.64±0.02	14.06±0.14	1.16±0.02
F5	27.67±0.94	0.47±0.05	0.53±0.04	11.32±0.12	1.13±0.05
F6	24.79±0.13	0.52±0.06	0.61±0.02	14.75±0.14	1.17±0.03
F7	27.75±0.42	0.43±0.03	0.51±0.04	15.69±0.13	1.19±0.04
F8	26.73±0.58	0.45±0.07	0.53±0.03	15.09±0.16	1.18±0.02
F9	24.23±0.45	0.54±0.04	0.64±0.05	15.63±0.12	1.19±0.02

Table 4: Swelling Index of Formulations

Formulation Code	Swelling Index*
F1	0.125
F2	0.150
F3	0.175
F4	0.136
F5	0.112
F6	0.120
F7	0.115
F8	0.126
F9	0.106

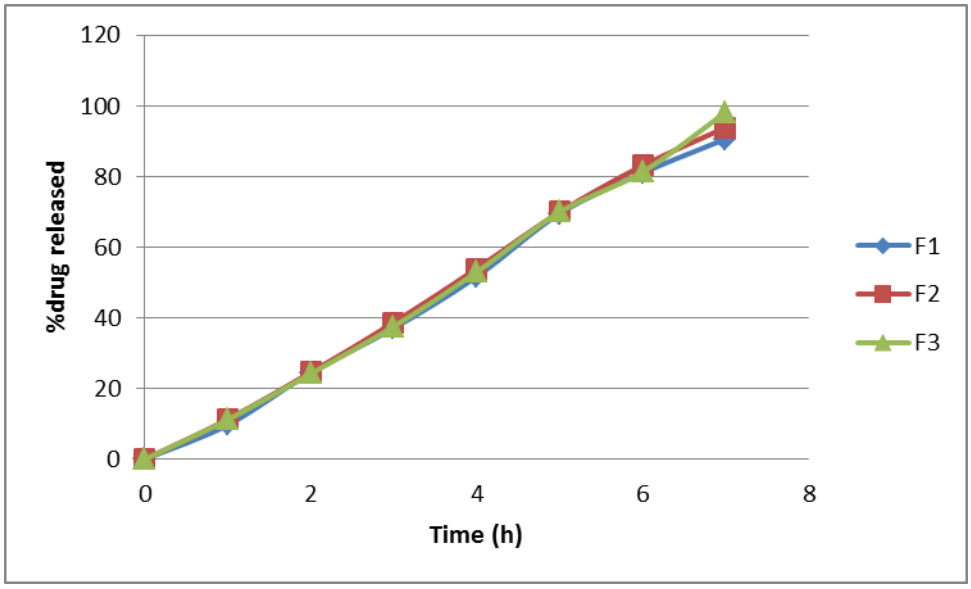

Figure 1: Dissolution profiles of F1, F2, F3

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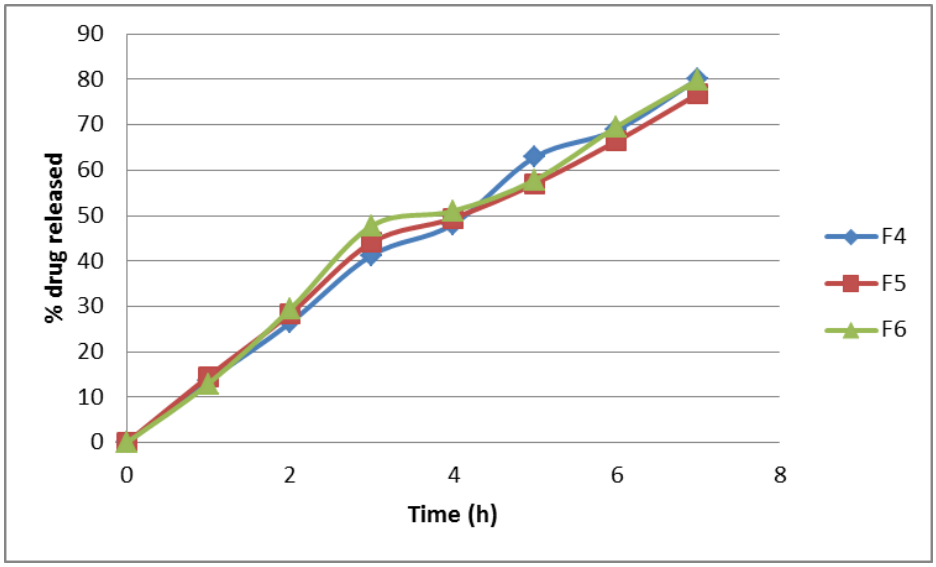

Figure 2: Dissolution profiles of F4, F5, F6

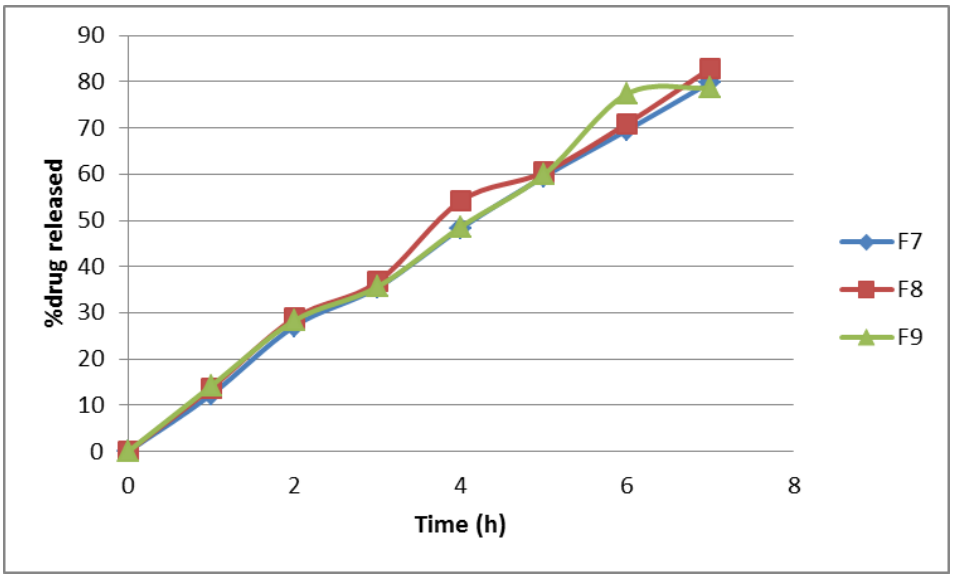

Figure 3: Dissolution profiles of F7, F8, F9

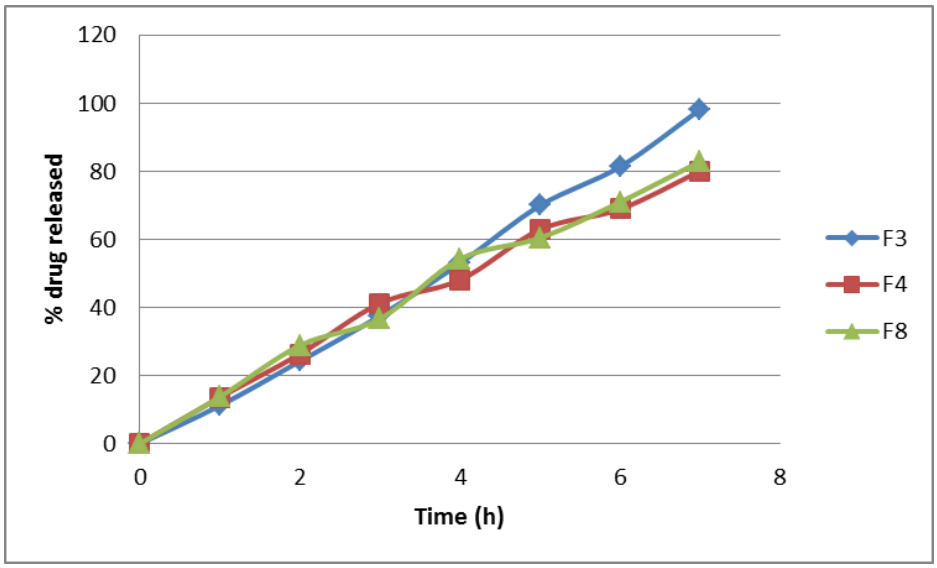

Figure 4: Dissolution profiles of F3, F4, F8

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Table 5: *In vitro* drug release data of bilayered buccal tablets formulations

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	9.71	11.31	11.17	13.61	14.57	12.95	12.31	13.75	14.18
2	24.49	24.58	24.23	26.33	28.35	29.32	27.1	28.84	28.31
3	37.09	38.67	37.54	41.22	44.07	47.7	35.48	36.7	35.64
4	51.69	53.962	52.96	48.09	49.42	51	48.28	54.22	48.6
5	69.52	69.96	69.96	62.87	57	57.82	59.47	60.42	59.91
6	81	83.07	81.34	68.87	66.36	69.52	69.52	70.97	77.36
7	90.62	93.89	98.15	80.07	76.79	79.88	79.88	82.88	78.65

Table 6: Drug Release Kinetics

Formulation	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Korsemeyer- Peppas (R^2)	n value
F1	0.9958	0.8835	0.897	0.9955	0.7541
F2	0.9979	0.8831	0.8997	0.9768	0.6459
F3	0.9973	0.7426	0.8877	0.9823	0.7279
F4	0.9913	0.9671	0.9419	0.9833	0.6668
F5	0.9793	0.979	0.9595	0.9837	0.6671
F6	0.9719	0.9347	0.9499	0.9904	0.5765
F7	0.9919	0.9579	0.9381	0.9912	0.6542
F8	0.9921	0.9579	0.9375	0.9915	0.7129
F9	0.998	0.9502	0.926	0.9882	0.7352

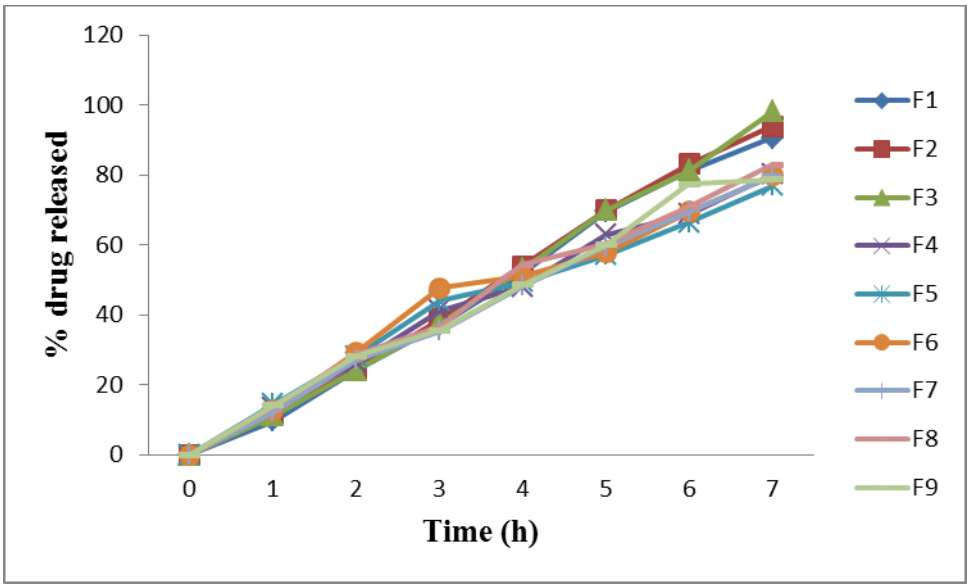

Figure 5: Dissolution profiles of bilayered buccal tablet formulations

Table 7: Stability studies

Formulation Code	Initial Drug Content	Storage Temperature	% Drug Content			
			2 weeks	4 weeks	6 weeks	8 weeks
F1	97.25	25±2ºC	98.09	97.95	97.81	97.92
		40±2ºC	98.01	97.91	97.24	96.98
F2	96.374	25±2ºC	97.37	97.49	97.76	96.30
		40±2ºC	96.17	95.32	95.51	94.28
F3	95.44	25±2ºC	96.91	96.52	96.78	96.36
		40±2ºC	96.79	95.86	95.41	94.50
F4	95.55	25±2ºC	96.34	96.43	97.25	96.84
		40±2ºC	96.22	96	95.40	94.27
F5	99.02	25±2ºC	100.72	100.43	100.25	100.23
		40±2ºC	99.75	99.45	99.24	98.87
F6	101	25±2ºC	101.82	102.15	102.54	102.23
		40±2ºC	102	101.89	101.75	100.91
F7	93.72	25±2ºC	94.09	95.95	95.81	94.92
		40±2ºC	94.01	93.91	93.77	93.59
F8	89.99	25±2ºC	91.22	92.56	92.62	92.88
		40±2ºC	92.69	91.52	90.43	88.95
F9	98.143	25±2ºC	98.25	98.12	97.93	97.97
		40±2ºC	98.21	987.93	97.98	97.82

CONCLUSION

The precompression parameters of the powder blends used for the preparation of immediate release layer and sustained release layer were in acceptable range of pharmacopeial specification with excellent flow and good compressibility. The sustained release layer of midazolam was prepared using polymers like HPMC, carbopol and ethyl cellulose in different ratios (1:1, 1:2 and 1:3) by wet granulation method. The physical parameters of midazolam sustained release layer were within the acceptable limit with good mechanical and handling and flow properties. Swelling index and *in vitro* drug release tests were carried out in phosphate buffer pH 6.8. The *in vitro* drug release study showed that the drug release was prolonged upto 7 hours using HPMC K15M, EC and carbopol 940P. Formulation F3 containing HPMC K15M in the ratio 1:3 gave sustained release profile comparatively better than the other formulations. The drug content of F3 was found to be 98.44%. Hence, an effective sustained release drug delivery system has been developed in the form of bilayer buccal tablets of midazolam for oral delivery. The results of the study also suggest that all the main objectives of the study were met and the formulation can be commercially exploited.

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