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FORMULATION DEVELOPMENT AND *IN-VITRO* EVALUATION OF MIDAZOLAM SOLID DISPERSIONS AND THEIR BUCCAL FLASH DISINTEGRATING FILMS

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Abstract:

The main objective of the present work is to prepare novel buccal flash disintegrating film inorder to by-pass the first pass metabolism, thus increasing its oral bioavailability. But the water solubility of the drug is poor, so inorder to increase its water solubility solid dispersions of midazolam was prepared using different carriers (Hydroxypropyl β-cyclodextrins, Poloxamer-188, PEG-4000, PEG-3350+Poloxamer-407) in the ratios of 1:3, 1:5. After the preparation of solid dispersions, the *in vitro* release study was performed in P^H 6.8 Phosphate buffer for 1 hour. The effect of carrier concentration was studied. It was observed that the solid dispersion with Poloxamer-188 in a ratio of 1:5 by Co-grinding technique was successful in fast release of drug when compared to the pure drug. The optimized solid dispersion is further used to prepare flash disintegrating buccal films using different grades of HPMC. It was observed observed that the formulation F3 was successful in fast release of the drug from the prepared buccal flash-disintegrating films.The FTIR study revealed that there was no chemical interaction between drug and excipients.

Keywords: Midazolam, Solid-Dispersions, Anti-Convulsant, Hydroxypropyl β-cyclodextrins, Poloxamer-188, PEG-4000, PEG-3350+Poloxamer-407, HPMC E-15LV, HPMC E-5, buccal flash-disintegrating films.

INTRODUCTION:

Usually Midazolam is given as a nasal syringe or buccal syringe for the treatment of stratus epilepticus in infants. But its administration requires skilled assistance. So for the ease of administration, Midazolam is to be prepared as buccal flash disintegrating films using hydrophilic film forming polymers like HPMC E-15LV, HPMC E-5 by solvent casting technique.

Midazolam is a derivative of the imidazobenzodiazepine group. Its mechanism of action is similar to other benzodiazepines. Midazolam has an anticonvulsant effect, a hypno-sedative effect, and an anxiolytic and muscle-relaxant effect. After intramuscular or intravenous administration anterograde amnesia of short duration occurs. Midazolam's effects are mediated by enhancement of Gamma Amino Butyric Acid (GABA) neurotransmission in limbic, thalamic and hypothalamic regions of the central nervous system (CNS). The anticonvulsant activity of midazolam is mediated by inhibition of the spread of seizure activity. Effects of midazolam resolve rapidlydue to fast metabolic transformation.

Secondly, it is belonging to Class-II drugs of BCS; thus has high permeability but poor solubility.

Various techniques have been used to improve the solubility/dissolution rate of poorly water-soluble drugs. Among them, the solid dispersion technique and complexation with cyclodextrinare most frequently used. In solid dispersions, hydrophilic polymers have commonly been used as carriers.According to this method, a drug is thoroughly dispersed in a water-soluble carrier by suitable method of preparation. The mechanism by which the solubility and the dissolutionrate of the drug are increased includes: firstly, the particle size of a drug is reduced to submicron size or to molecular size in the case where the solid solution is obtained. Theparticle size reduction generally increases the rate of dissolution; secondly, the drug is changedfrom crystalline to amorphous form, the high energetic state which is highly soluble; finallythe wettability of the drug particle is improved by the dissolved carrier.

MATERIALS AND METHODS

Materials:

Midazolam (is a gift sample from Celon labs, Hyderabad), Hydroxy propyl β-cyclodextrins (Roquettepharma Pvt. Ltd), Poloxamer-188 (Sigma - Aldrich), Poloxamer-407 (Sigma - Aldrich), PEG-4000 (LobaChemie Pvt.Ltd, Mumbai, India), and PEG-3350 (Sun pharmaPvt. Ltd, Mumbai, India), HPMC E-15LV & E-5(LobaChemie Pvt. Ltd, Mumbai, India)and all other chemicals were analytical grade from my institute.

Methods:

Preparation of Solid Dispersions:[16]

Solid dispersions were prepared by solvent evaporation method,co-grinding method & fusion method.

Solventevaporation technique: The required amount of Midazolam(10mg) and carriers in the ratio of 1:3, and 1:5 were dissolved in sufficient amount of methanol and kept on sonication for up to 20min. The solvent from the solution was removed at 45°C with continuous stirring to obtain dry mass. Dried mass was pulverized through 40'mesh sieve and stored in desiccator until used for further studies.

Co-grinding technique: The required amount of Midazolam(10mg) and carriers in the ratio of 1:3, and 1:5 were dissolved in sufficient amount of methanol in glass mortar and triturated for up to 30min till the paste like consistence is obtained. The solvent from the solution was removed at 45°C in vacuum owen to obtain dry mass. Dried mass was pulverized through 40'mesh sieve and stored in desiccator until used for further studies.

Fusion method: The required amount of Midazolam (10mg) with various carriers in the ratio of 1:3 and 1:5 were prepared by melting method. In this method the polymer is melted at over a thermostatically controlled hot plate at its respective melting point and the drug was incorporated into the molten carrier mass. The blend was heated at the corresponding temperature for 5 minutes, followed by flash cooling on an ice bath. The solid dispersions thus obtained,were dried in oven at 30°C to remove moisture ifpresent. The dried solid dispersion was pulverized through 40'mesh sieve and stored in the desiccatorfor further use. The dispersions obtained were tacky.

Formulation of Midazolam solid dispersion with different carriers showed in the (table:1)

Preparation of standard curve:

10mg of drug was dissolved in 10ml methanol to produce 1000µg/ml stock solution. From the stock solution, 1ml is pipetted in to 100ml volumetric flask and made up to the volume with P^H 6.8 phosphate buffer and further dilutions were made to produce different concentrations from 5µg/ml-30µg/ml.Standard solutions were then analyzed by UV spectrophotometer (Thermo labs, Evolution 201) at 276 nm and absorbance was noted.Then the absorbance values were plotted against drug concentration and standard curve of Midazolam was produced (Figure 1).

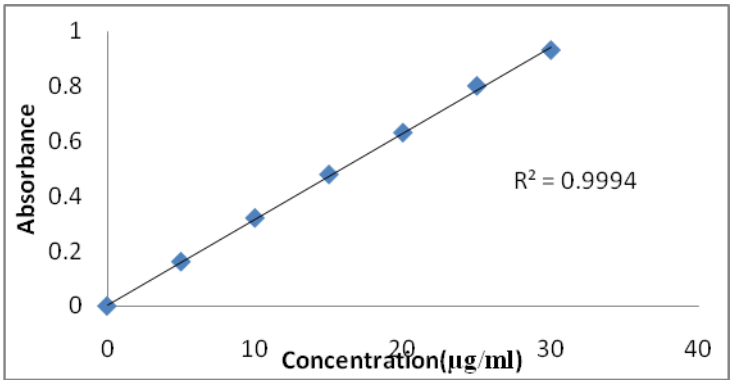


Figure 1. Standard curve of Midazolam in P^H 6.8 phosphate buffer

Evaluation of Solid dispersions:

FTIR Studies:IR spectra for Midazolam and Solid dispersions were recorded in aFourier transform infrared spectrophotometer (BRUKER). The functional groups are not altered during

mixing with carriers. -NH stretching=3300-3500 cm^{-1}, C-H stretching-3500-3200 cm^{-1} are not changed with combination of carriers.

The FTIR revealed that there is no interaction between drug and carrier.

Drug content:

Drug content was determined by dissolving solid dispersion equivalent to 10mg of Midazolam was dissolved in freshly prepared Phosphate buffer pH-6.8 in a 100 ml volumetric flask. Then the volume was made up to 100 ml with Phosphate buffer pH-6.8. From this 1 ml was taken and suitable dilutions were made to get 1 µg/ml with Phosphate buffer pH-6.8. The absorbance of the resulting solution was measured at 276 nm against blank (Phosphate buffer pH-6.8)..The results were observed in table-2.

In vitro drug release studies*:*[5,7]

In-vitro dissolution studies of midazolam in pure drug form and solid dispersions were performed by using the US Pharmacopoeia (USP) model digital tablet dissolution test apparatus-2 (Lab India, DISSO 2000) at the paddle rotation speed of 75 rpm in 900 mL of phosphate buffer pH 6.8. The dissolution rate was studied by placing midazolam 10 mg and solid dispersions equivalent to 10 mg of drug on the surface of dissolution medium. A 5 ml aliquot was withdrawn at different time intervals, filtered (through 0.45µ) and replaced with 5 ml of fresh dissolution medium. The samples were estimated for dissolved midazolam by measuring absorbance at 276nm.The results were observed in table-3, and graph-1.

XRD Studies:

The powder XRD of the Pure midazolam and Solid Dispersions (midazolam with poloxamer-188) was recorded using an X-ray Diffractometer (Diffractometer system, XPERT-PRO) using Cu radiation generated at 40Kv and 30 mA and scanning rate was 2°/min over a 2Ø range of 10-80.Best solid dispersiondetermined was scanned under XRD.

Powder X-RD patterns of pure midazolam shows 46 major peaks at diffraction angles(2θ) of 10.83^{o}, 13.91^{o}, 15.10^{o}, 17.36^{o},…… 77.52^{o} , indicating its crystalline nature.

But the intensity of peaks displayed in XRD pattern of pure midazolam disappeared in XRD pattern of midazolam-poloxamer188 solid dispersion indicating the existence of amorphous solid state of midazolam-poloxamer 188. The results were observed in graph-2.

FORMULATION AND EVALUATION OF BUCCAL FLASH DISINTEGRATING FILMS:

Evaluation of Midazolam solid dispersion and polymers physical mixtures by FTIR studies:

The infrared absorption spectra of optimized solid dispersion, physical mixture of polymer (HPMC E5, HPMC E15) and drug were performed for polymer drug interaction studies between 4000 $cm^{-1}$to 400 $cm^{-1}$by KBr pellet method.

The FTIR revealed that there is no interaction between drug and carrier.

Formulation of Buccal Flash Disintegrating Films:

The oral fast dissolving films were prepared by solvent casting method using HPMC E5, HPMC E 15, as film base with different concentrations. PEG-400 was used as plasticizer, mannitol was

used as sweetening agent, and citric acid was used as saliva stimulating agent. Polymers, mannitol, citric acid and PEG 400 were added to distilled water and stirred for 2 minutes on a magnetic stirrer. Solid dispersion of drug solution was added to the above solution under continuous stirring for 2 minutes and sonicated for 5 minutes to remove air bubbles. This solution was casted on a petri dish and dried in hot air oven at 40º C for 12 hours. The films were carefully removed from petri dish, checked for any imperfections and cut into required size. The samples were stored in a desiccator for further analysis.

Table no: II. Formulation table

INGREDIENTS	**F1**	**F2**	**F3**	**F4**
DRUG SD	60	60	60	60
HPMC E15 LV	100	200	----	----
HPMC E5	----	----	100	200
PEG-400(ml)	0.1	0.1	0.1	0.1
MANNITOL	10	10	10	10
CITRIC ACID	2	2	2	2
WATER(ml)	10	10	10	10

Thickness uniformity:

All the films were evaluated for thickness by using thickness gauge with a least count of 0.01mm. The thickness was measured at three different spots of the films and the average was taken.

Folding endurance:

The folding endurance was measured manually for the prepared films. The flexibility of films can be measured quantitatively in terms of folding endurance. A strip of film was cut (approximately 3x2cm^2) and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

Surface pH:

An acidic or alkaline pH may cause irritation to the oral mucosa, it is determined to keep the surface pH of fast dissolving film as close to neutral as possible. A combined pH electrode is used for this purpose. Film was slightly wetted with water and pH was measured by bringing the electrode in contact with the surface of oral film. This study is performed on three films of each formulation and mean ± SD was calculated.

Drug content uniformity test:

3x2 cm^2 film was kept in 25 mL of pH 6.8 phosphate buffer. This solution was sonicated for 5 minutes and filtered. Drug content was determined spectroscopically after appropriate dilution at 276 nm using UV visible spectrophotometer.

***In vitro* disintegration test:**

This test was performed by placing the film in a glass petri dish containing 10 mL of pH 6.8 phosphate buffer. The time required for the film to break and disintegrate was noted as *in vitro* disintegration time.

***In vitro* dissolution studies:[19]**

The *in vitro* drug dissolution was carried out in 500 mL of pH 6.8 phosphate buffer at 37±0.5ºC, using USP Apparatus-I at a stirring speed of 100 rpm. The samples were withdrawn at a time interval of one minute. Fresh buffer solution was replaced immediately after each sampling. The absorbance was measured spectroscopically at a λ max of 276 nm. The results were observed in table-5.

Scanning Electron Microscope:

Scanning electron microscope (SEM) images of the buccal film surface were obtained using the scanning electron microscope (JSM-6100 SEM). The film was cut into smaller pieces and was mounted on a metal stub with double-sided adhesive tapes. Best formulation determined was scanned using SEM.

Results and discussions:

- Solid dispersion (SD_8) containing 1:5 ratio of drug**:** poloxamer-188 showed the best release with a cumulative release of 106% as compared to 51.40% with the pure drug.
- In vitro drug release studies reveal that there was marked increase in dissolution rate of midazolam from all the solid dispersions when compared to pure midazolam itself.
- From the invitro dissolution data of buccal flash disintegrating films, it was observed that the F_3formulation gives the very rapid release of Midazolam when compared to other formulations.
- From the scanning electron micrographs, the surface morphology of buccal film was observed to be smooth without any coarseness and imperfections.

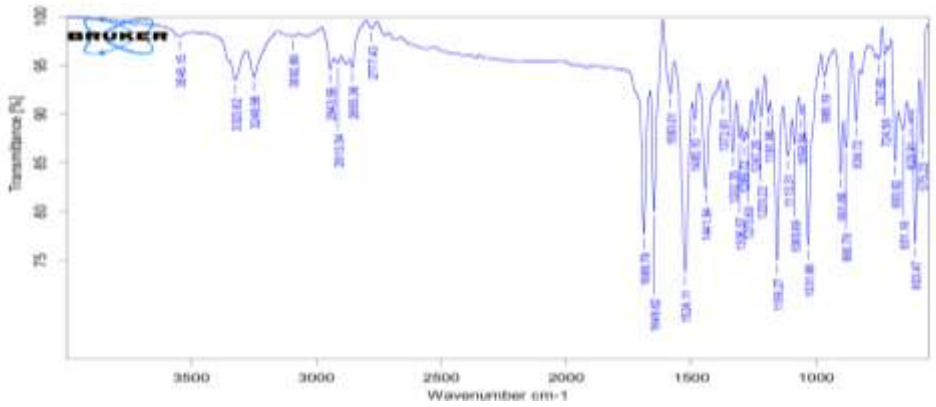
Conclusion:

The increase in dissolution rate is in the order of POLOXAMER-188>PEG-3350+POLOXAMER-407>PEG-4000>HP β-CYCLODEXTRIN. Among the solid dispersion methods, Co-grinding method was found to be more suitable for improving solubility of the drug. The dissolution rate of midazolam in solid dispersion was strongly dependent on the relative concentration of the carrier. As the concentration of the carrier in the solid dispersion increased, the dissolution rate also increased.

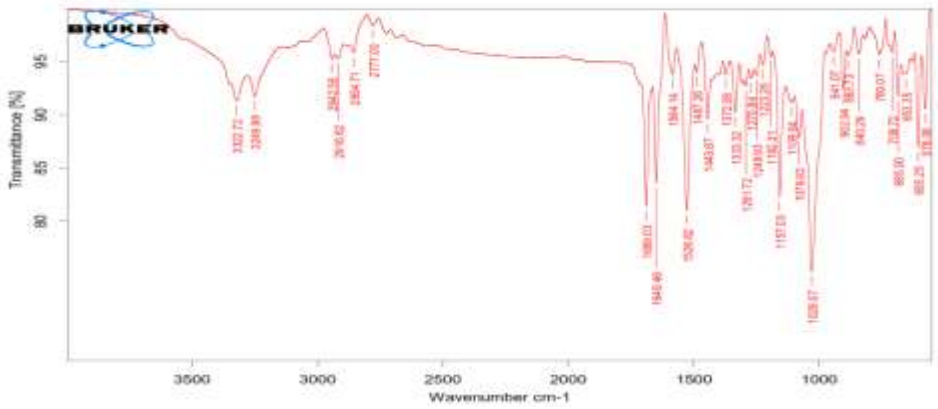
In-vitro dissolution for formulation F3 was best when compared to other formulations. The % release was found to be 98.84 within 4 min.

FTIR studies:

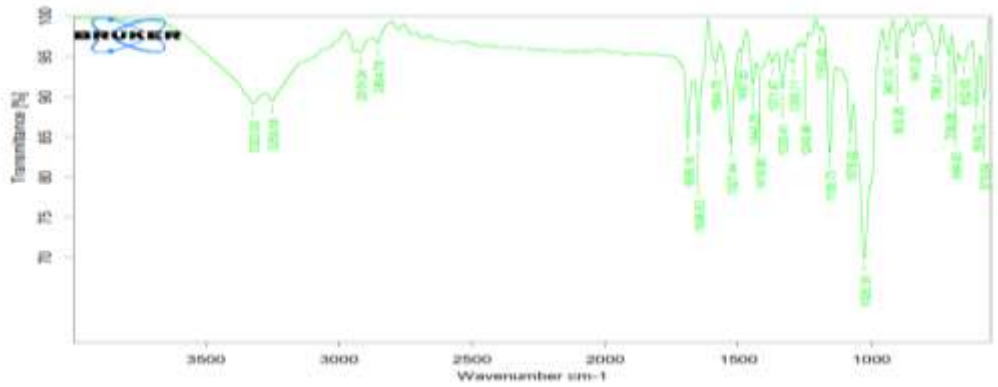
FTIR of Midazolam



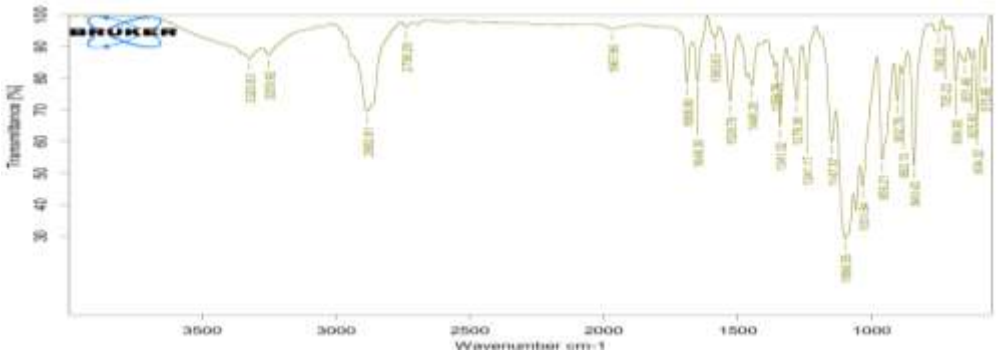
FTIR of Midazolam-Hydroxy propyl β-cyclodextrin solid dispersion (solvent evaporation)



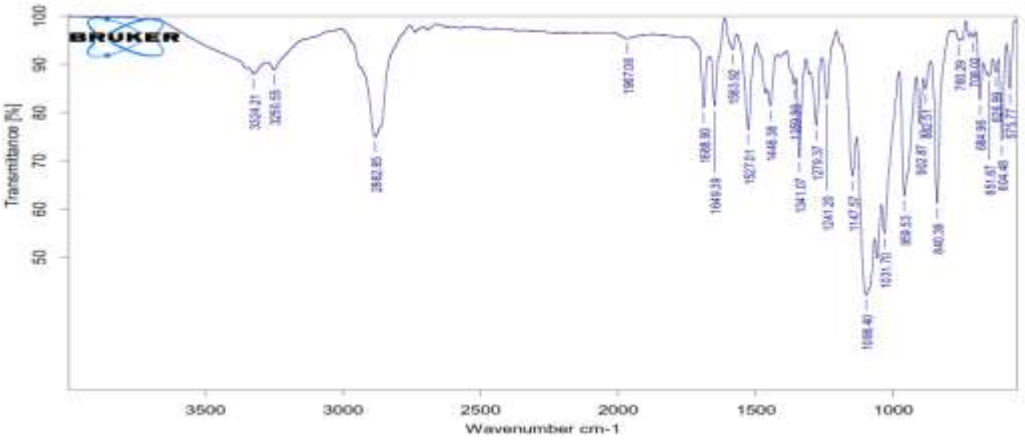
FTIR of Midazolam-Hydroxy propyl β-cyclodextrin solid dispersion (co-grindng)



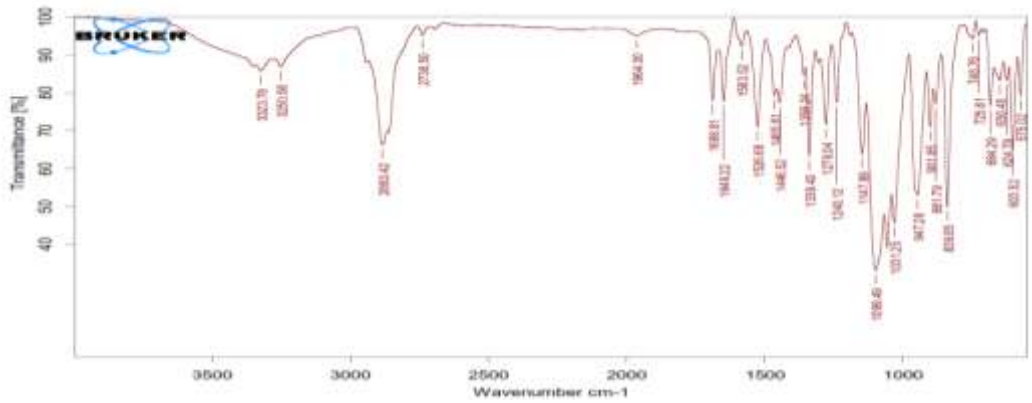
FTIR of Midazolam-Poloxamer 188 solid dispersions (solvent evaporation)



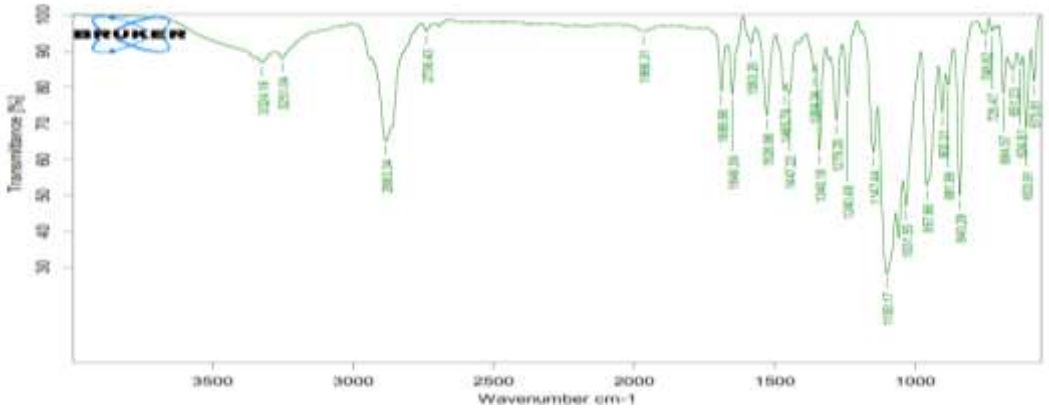
FTIR of Midazolam-Poloxamer 188 solid dispersions (co-grinding)



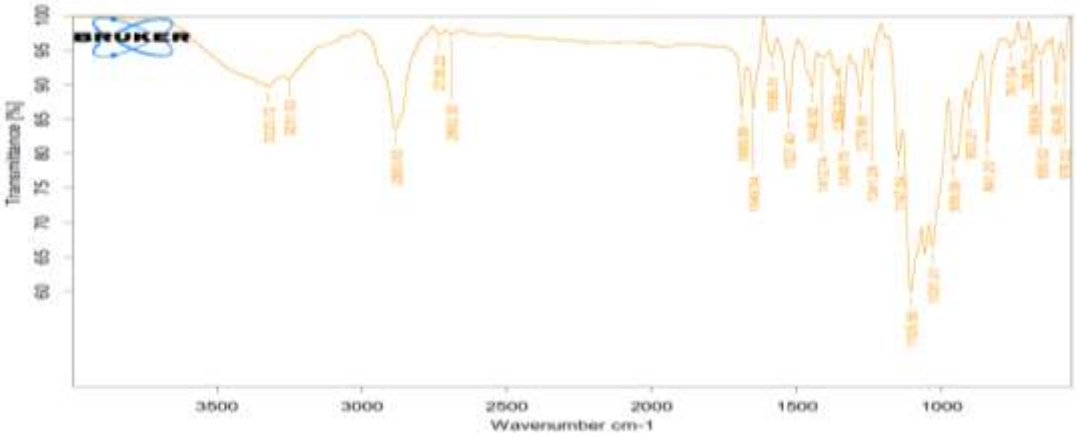
FTIR of Midazolam-PEG 4000 solid dispersions (fusion method)



FTIR of Midazolam-PEG 3350+Poloxamer 407



FTIR of SD_8+HPMC E15 LV



FTIR of SD_8+HPMC E-5

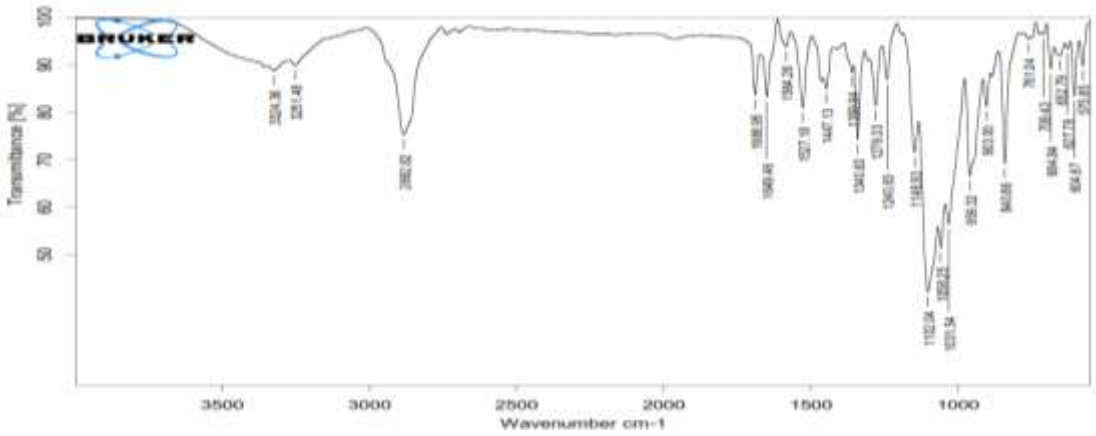


Table: 1.Composition of Midazolam solid dispersion with different carriers

Solid Dispersion composition	Method	Drug: carrier ratio	Formulation code
Midazolam: Hydroxypropyl β-cyclodextrins	Solvent evaporation method	1:3	SD_1
		1:5	SD_2
	Co-grinding method	1:3	SD_3
		1:5	SD_4
Midazolam: Poloxamer-188	Solvent evaporation method	1:3	SD_5
		1:5	SD_6
	Co-grinding method	1:3	SD_7
		1:5	SD_8
Midazolam: PEG4000	Fusion method	1:3	SD_9
		1:5	SD_{10}
Midazolam: PEG3350+Poloxamer 407	Fusion method	1:3	SD_{11}
		1:5	SD_{12}

Table: 2. Drug content of prepared solid dispersions

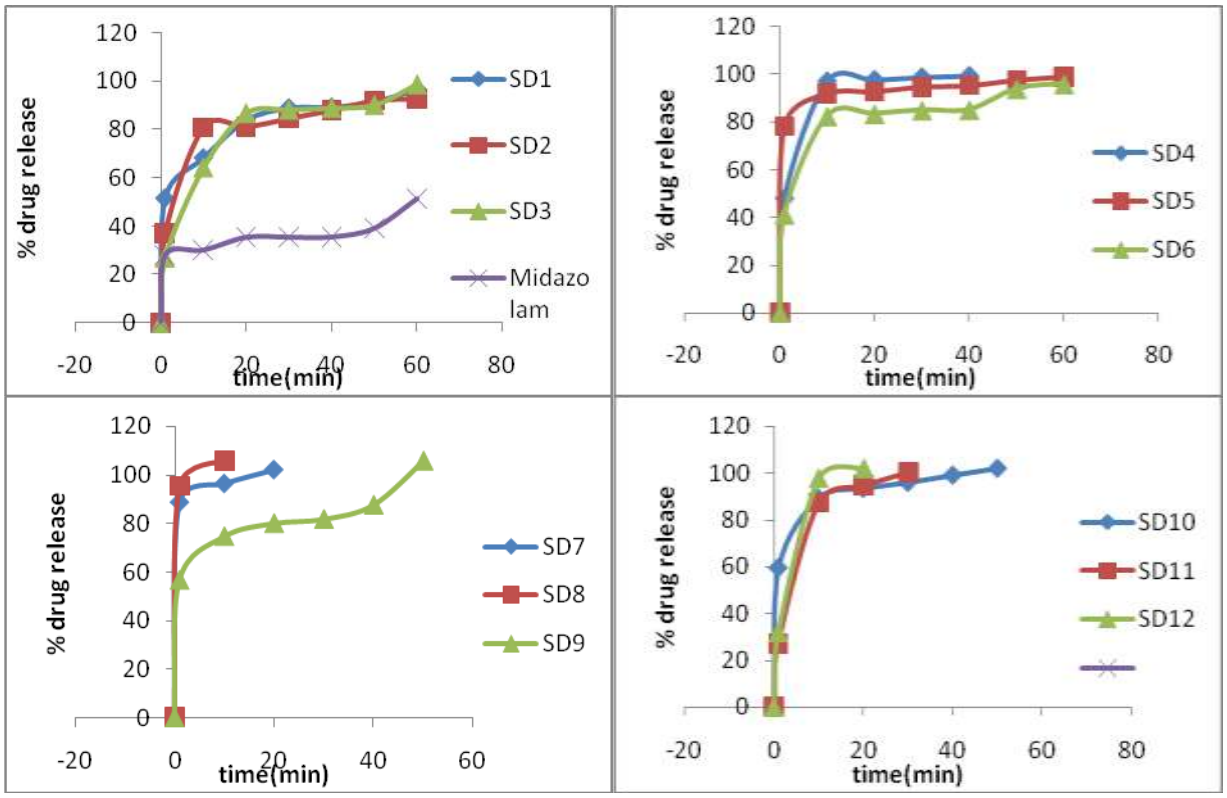
Formulation code	Drug content
SD_1	99.21±1.4
SD_2	99.6±1.1
SD_3	99.5±1.1
SD_4	99±1.9
SD_5	98.23±1.2
SD_6	99.83±1.1
SD_7	99±1.2
SD_8	100.3± 0.5
SD_9	99.7± 1.9
SD_{10}	96.9 ± 1.4
SD_{11}	98.8 ± 1.8
SD_{12}	98.1± 1.1

Table: 3. Invitro drug release study of prepared solid dispersions

Time (min)	% Drug release												
	Midazolam	SD_1	SD_2	SD_3	SD_4	SD_5	SD_6	SD_7	SD_8	SD_9	SD_{10}	SD_{11}	SD_{12}
1	28.2±0.48	51.68±0.77	37.2±0.64	27.1±0.96	48±0.56	78.2±0.32	41.23±0.32	88.6±0.9	95.4±1.09	56.76±1.04	59.5±0.91	27.1±0.71	31.9±1.24
10	30.2±0.83	68.3±0.63	80.7±0.74	64.4±0.63	97.1±1.24	92±0.83	82.46±0.84	96.3±0.63	106±0.11	74.8±1.32	89.2±0.78	87.2±0.78	97.7±1.05
20	35.3±0.31	83.88±0.	81±0.46	86.9±0.2	97.7±1.0	92.9±0.7	83.5±0.9	102±0.1		80.2±0.9	93.4±0.4	94.6±0.8	101.9±0.27

		25		8	5	5		9		2	3	2	
30	35.5±0.43	88.9 ±0.6 2	84.4 ±0.3 8	88.3 ±0.4 1	98.8 ±0.6 7	94.8 ±0.7 8	85± 0.86			81.9 0±1	96±1 .05	100. 3±0. 36	
40	35.58±0.5 9	89.2 ±0.4 4	87.8 ±0.5 7	89± 0.60	99.4 ±0.5 4	95.4 ±0.5 9	85.2 ±0.9 4			87.8 ±1.1 5	99.1 ±1.0 3		
50	39.2±0.75	91.5 0±0. 49	91.7 ±0.3 2	90.3 ±0.7 0		97.7 ±0.8 9	94± 1.02			106 ±0.1 8			
60	51.40±0.7 8	96.5 ±0.5 6	92.6 ±1.0 5	98.8 ±0.5 6		99.1 ±1	96± 1.14						

Graph: 1



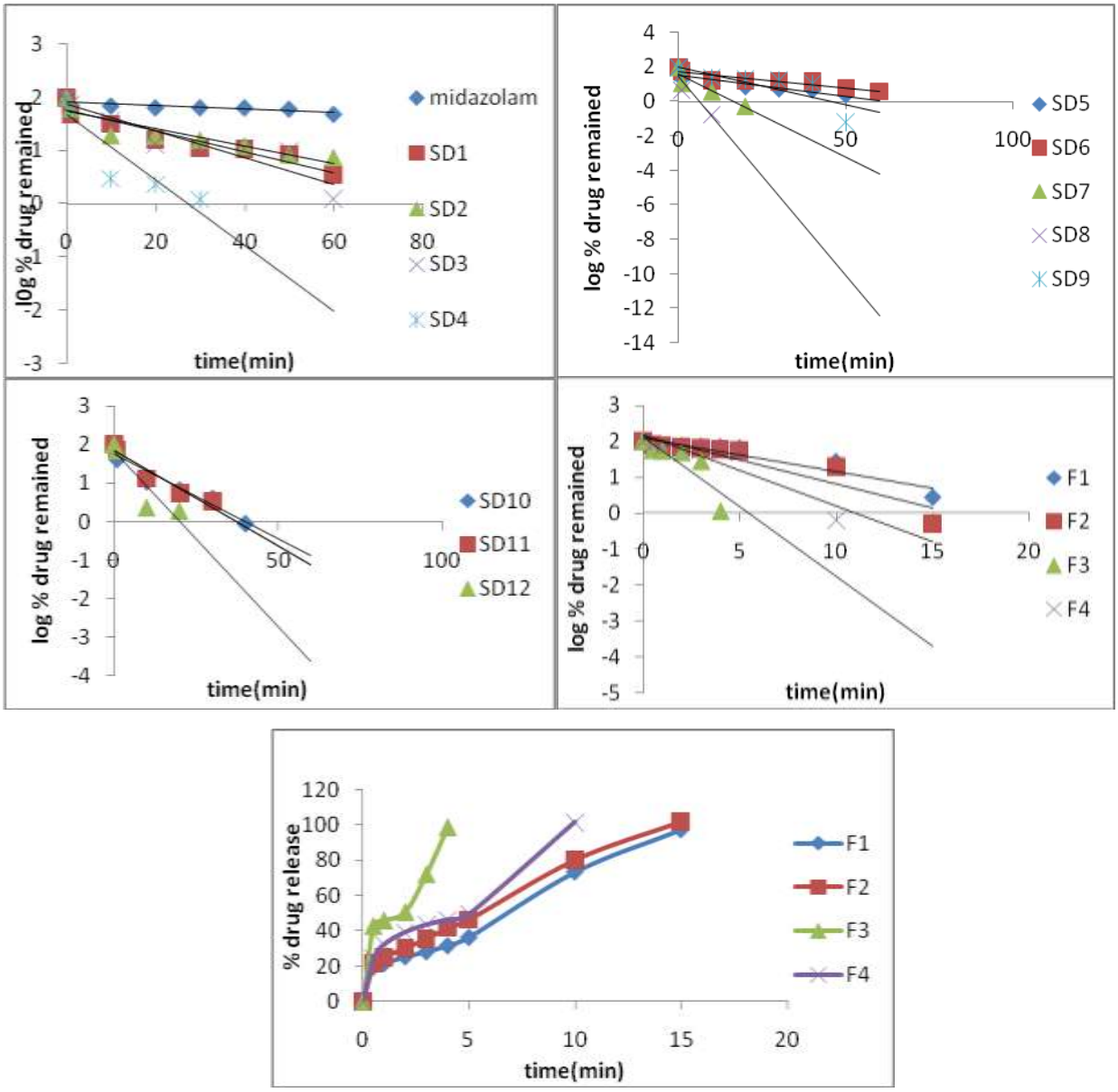


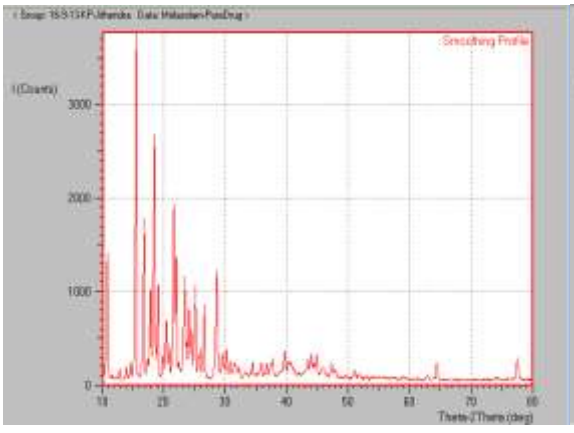
Table: 4. Evaluation of parameters of prepared buccal flash-disintegrating films

formulation	Thickness(mm)	Folding endurance	Surface pH	Drug content	Invitro disintegrating time
F1	0.60	74±1	6.6±0.05	98.5 ±0.11	18±1
F2	0.80	83±2	6.67±0.05	96.5 ±0.11	24±1
F3	0.87	96±2	6.7±0.1	98.4 ±0.2	17±1
F4	0.83	108±1	6.73±0.07	99.2 ±0.2	19±1

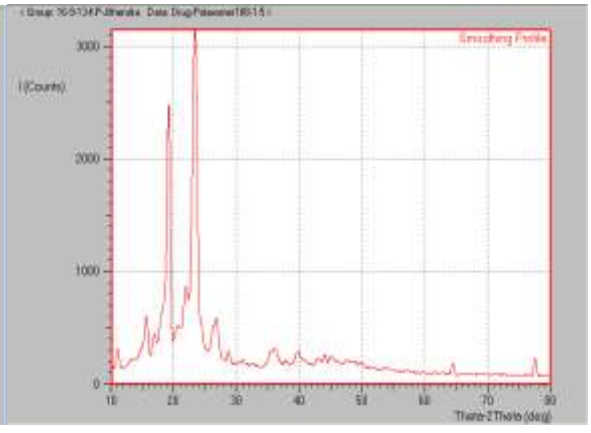
Table: 5. Invitro drug release study of prepared buccal flash disintegrating films

Time	% Drug release			
	F1	**F2**	**F3**	**F4**
30 sec	19.76±1.5	21.65±0.65	42.99±1.0	24.63±0.71
1 min	21.65±0.98	25.26±1.83	46.12±0.1	32.47±0.58
2 min	25.41±0.5	30.43±0.24	50.83±0.73	39.38±0.22
3 min	28.24±1.23	35.61±1.93	72.17±3.09	43.61±0.31
4 min	31.69±1.43	41.89±1.01	98.84±1.80	46.44±0.64
5 min	36.40±1.12	46.44±1.39		49.42±0.70
10 min	73.4±2.5	80.33±2.33		101.6±1.61
15 min	97.28±2.19	101.98±2.08		

Graph: 2. XRD of optimized solid dispersion (SD_8)

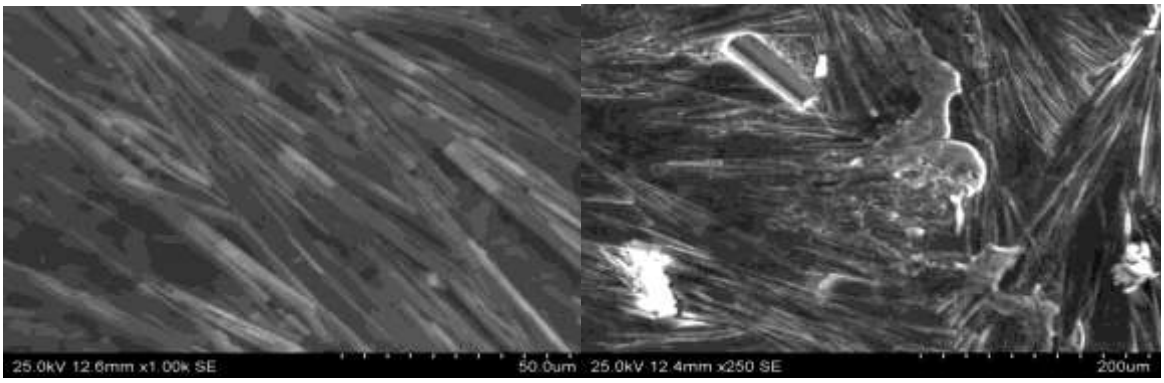


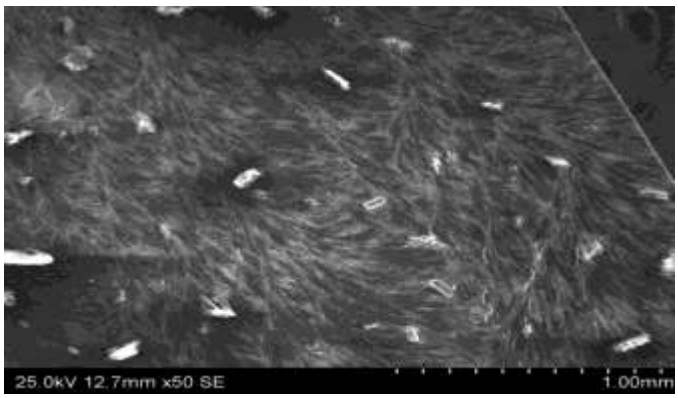
XRD of Midazolam Solid Dispersion (SD_8)



XRD of Midazolam-Poloxamer 188(1:5)

SEM: Scanning Electron Microscopy of optimized buccal flash disintegrating films (F3)





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