An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

ENHANCEMENT OF THE SOLUBILITY OF MIDAZOLAM USING SOLID DISPERSION TECHNIQUE AND INCORPORATING IT IN BUCCAL FILM

Amiyakanta Mishra*[1], Chinmaya Keshari Sahoo[1], Amaresh Prusty[1]

[1]Department of Pharmaceutics, College of Pharmaceutical Sciences (Affiliated to Biju Patnaik University of Technology), Puri, Odisha.

***Corresponding author E-mail:** amiyar@rediffmail.com

ARTICLE INFO

Key Word
Solid dispersion,
Buccal film,
Solvent Evaporation method,
Solvent casting technique

ABSTRACT

Solid dispersion of midazolam was prepared by using carrier Pluronic F127. Solvent evaporation method was used for preparation of solid dispersion. Evaluation of solid dispersion was carried out including *in vitro* dissolution studies, drug content, and solubility. Solvent casting technique is used to prepare buccal film by incorporating the optimized formulation of solid dispersion. Developed buccal films were evaluated for thickness, drug content, surface pH, in vitro drug release study etc.Optimized formulation F4 was carried out for accelerated stability study showing no significant changes in drug content, and drug release on storage of 6 months.

INTRODUCTION

Amongst the various routes of drug delivery, oral route [1] is perhaps the most preferred to the patient and the clinician alike. However, per oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the gastrointestinal tract (GIT) that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosae are considered as potential sites for drug administration. Buccal film offer greater flexibility [2] and comfort than the other dosage forms. In addition, a film can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva. Buccal route drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass [3] hepatic metabolism leading to high bioavailability. It has low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer, pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action. Midazolam [5] is used for the treatment of stratus epilepticus in infants. 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. The anticonvulsant activity of midazolam is mediated by inhibition of the spread of seizure activity. Midazolam is belonging to Class-II drugs of BCS; thus has high permeability but poor solubility. Various techniques have been used to improve the solubility of poorly water-soluble drugs. Amongst them solid dispersion [6] technique is most frequently used. In solid dispersions, hydrophilic polymers have commonly been used as carriers to enhance solubility of the drug. Then solid dispersion containing Midazolam is to be prepared as buccal flash disintegrating films using hydrophilic film forming polymers like HPMC E 15 by solvent casting technique.

MATERIALS AND METHODS

Materials

Midazolam was obtained from Sun Pharmaceuticals Pvt. Ltd. India., Citric acid, and HPMC were purchased from S.D. Fine Chemicals Ltd, Mumbai, India., Microcrystalline cellulose(MCC) and pluronic F127 were purchased from Signet Pharma, Mumbai, India. PEG-400 (LobaChemie Pvt.Ltd, Mumbai, India), All other solvents and reagents used were of analytical grade.

Methods

Preparation of solid dispersion: The solvent evaporation method is used. Solid dispersions [7] were prepared with different ratio of drug and carrier. Methanol is used as solvent. 4 solid dispersions were made. Weighed amount of midazolam, and Pluronic F127 (Carrier) was dissolved in required amount of methanol. The above mixture was sonicated for 20 mins which forms a solution. Now, this solution was kept on magnetic stirrer at 45ºC to evaporate the solution which form a dry mass called as solid dispersion. So, formed dry mass was pulverised.

Incorporation of solid dispersion (SD) buccal film and its preparation

Solvent casting technique is used for preparation of solid dispersion buccal film. The pulverised solid dispersion or optimised solid dispersion was used to prepare a buccal film. Weighed amount of solid dispersion, HPMC E15, Mannitol, Citric acid was dispersed in water & PEG400 mixture used as vehicle to disperse. The dispersion was stirred & kept in sonicator for 15-20mins to remove air bubbles. Finally, the solution is poured into petri dish & kept it for 24 to 48 hrs to form a film. The formulation table is as shown in table.

EVALUATION OF SOLID DISPERSION AND BUCCAL FILMS

FTIR Study

IR spectra for Midazolam and Solid dispersions were recorded in a Fourier transform infrared spectrophotometer (BRUKER).

Characterization of solid dispersions

Micromeritic characterization Solid dispersion of granules

The prepared granules [8] were evaluated for pre compression parameters such as angle of repose, bulk density, tapped density and compressibility index (Carr's index).Fixed funnel method was used to estimate angle of repose. The bulk density and tapped density were evaluated by bulk density apparatus (Sisco, India).

The Carr's index [9] is calculated by the following formula.

$$\% \text{ Carr's index} = \frac{etap - ebulk}{etap} \times 100 \ldots\ldots (1)$$

Where e_{tap} is the tapped density of granules and e_{bulk} is bulk density of granules.

According to the specifications the Carr's index values between 5-15 indicates excellent flow whereas between 12-16 indicates good flow. Values between 18-21 indicates fair passable where as between 23-35 indicates poor and values between 33-38 indicates very poor and greater than 40 indicates extremely poor. Hausner's ratio was calculated by the taking the ratio of tapped density to the ratio of bulk density. According to specifications values less than 1.25 indicate good flow (= 20% of Carr's index) whereas greater than 1.25 indicates poor flow(=33% of Carr's index).

Physical characterization of solid dispersion

Solubility studies: The saturation solubility[10] of pure Midazolam, physical mixtures and solid dispersions were determined and compared with each other. The known excess samples (Midazolam solid dispersions, and pure Midazolam) were added to 5 ml of pH 6.8 phosphate buffer and these samples were rotated in a water bath (37 ± 0.5°C) for 48 hours. The samples were then filtered through 0.45 µm membrane filter, suitably diluted, and analyzed by UV-Visible spectrophotomer (Shimadzu Corporation, Japan) at 276 nm wavelength.

Drug content

The drug content in each solid dispersions [11] and physical mixture was determined by the UV spectroscopic method. An accurately weighed quantity of solid dispersion or physical mixture, equivalent to 100 mg of Midazolam, was transferred to a 100 mL volumetric flask containing 5 mL of methanol and dissolved. The volume was made up to 100 mL with pH 6.8. The solution was filtered and the absorbance was measured after suitable dilutions by using UV-VIS spectrophotomer (Shimadzu Corporation, Japan) at 276 nm wavelengths.

Table 1: Formulation batches of midazolam solid dispersion

Batch codes	Midazolam (mg)	Pluronic F127 (mg)	Drug: Carrier
SPF1	500	500	1:1
SPF2	500	1000	1:2
SPF3	500	1500	1:3
SPF4	500	2000	1:4

Table 2: Formulation of buccal films

Ingredients	F1	F2	F3
SD (SPF4) (mg)	50	50	50
HPMC E15 (mg)	150	100	50
Mannitol (mg)	10	10	10
Citric acid (mg)	2	2	2
PEG400 (ml)	0.1	0.1	0.1
Water (ml)	q.s	q.s	q.s

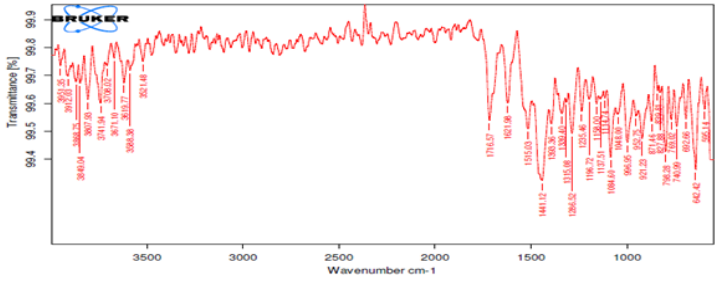

Figure 1: FTIR spectra of midazolam

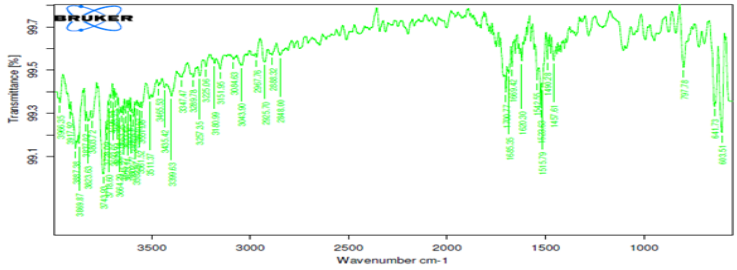

Figure 2: FTIR spectra of Pluronic F127

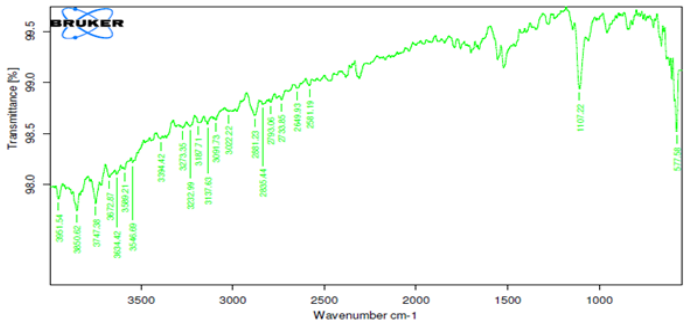

Figure 3: FTIR spectra of optimized SD SPF4

Table 3: Micromeritic characterization of SD formulations

Batch codes	Angle of repose (degree) ± S.D	Bulk density (gm/ml)± S.D	Tapped density (gm/ml)± S.D	Carr's Index (%) ± S.D	Hausner's Ratio± S.D
SPF1	29.11±0.08	0.519±0.07	0.557±0.08	6.82±0.08	1.07±0.06
SPF2	28.56±0.06	0.515±0.08	0.554±0.06	7.57±0.08	1.07±0.06
SPF3	26.32±0.07	0.514±0.06	0.559±0.08	8.05±0.06	1.08±0.08
SPF4	25.20±0.06	0.517±0.08	0.566±0.12	8.65±0.11	1.09±0.06

N.B: All values are expressed as mean ± S.D, [a] n = 3

Table 4: Physical evaluation

Batch codes	Solubility (mg/ml)	Drug content (%)	Yield (%)
Pure drug	0.0098 ±0.08	.....	.....
SPF1	0.011 ±0.08	95.82 ±0.07	93.42 ±0.08
SPF2	0.018 ±0.06	96.9 ±0.08	95.11 ±0.06
SPF3	0.029 ±0.07	97.75 ±0.06	96.04 ±0.08
SPF4	0.041 ±0.06	99.13 ±0.08	98.44 ±0.12

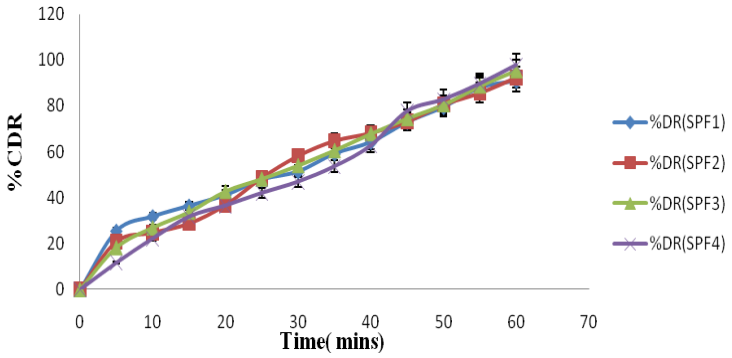

Figure 4: *In vitro* release profiles showing midazolam release from various fabricated formulations SPF1-SPF4 (n=3)

Table 5: Evaluation of parameters of prepared buccal flash-disintegrating films

Batches	Thickness (mm)	Folding endurance	Surface pH	*In vitro* disintegrating Time (sec)	Drug content (%)
F1	0.87 ± 0.16	140 ± 0.54	6.09 ± 0.12	22 ± 0.15	95.9 ±0.08
F2	0.84 ± 0.18	143± 0.62	6.69 ± 0.27	20 ± 0.23	96.85 ±0.09
F3	0.86 ± 0.11	156± 0.72	6.77 ± 0.28	18 ± 0.26	99.03 ±0.11

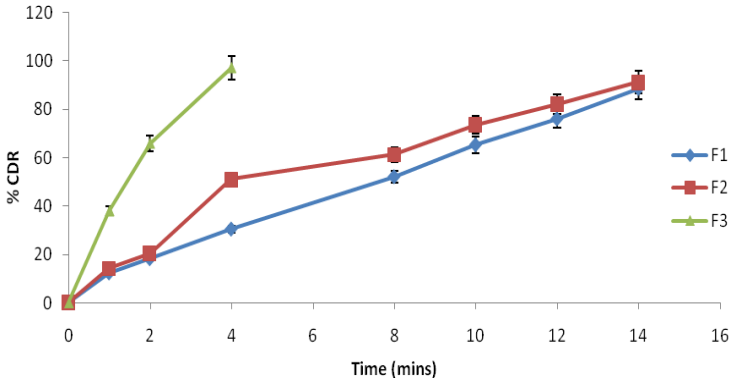

Figure 5: *In vitro* dissolution profile of batches F1-F3 as mean ±standard deviation; n=3)

Percentage Yield

To determine the efficiency of solid dispersion production percentage yield [12] was calculated. In this method preweighed solid dispersions were collected to determine practical yield. The percentage yield can be calculated using the given equation 2

$$\% \text{ Yield} = \frac{Practical\ yield}{Theoretical\ yield} \times 100 \ldots\ldots\ldots (2)$$

***In vitro* dissolution study**

Dissolution studies were performed in pH 6.8 phosphate buffer containing 900ml at 37 ± 0.5°C, using USP type-II apparatus with paddle rotating at 75 rpm. Sample of pure Midazolam, solid dispersions as well as

physical mixtures, each containing 10 mg equivalent of Midazolam were subjected to dissolution. Aliquots of 5 ml were withdrawn at time intervals of 10, 20, 30, 40,50, and 60 min were filtered and replaced with 5 ml of phosphate buffer pH 6.8. The samples were estimated for absorbencies of dissolved drug scanned at λmax 276 nm by using UV. The percentage cumulative drug release (% CDR) was calculated.

Evaluation of buccal films

Thickness uniformity

All the films [13] were evaluated for thickness by using thickness gauge with a least count of 0.01 mm. 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 [14]. 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.

***In vitro* disintegration test:** This test was performed by placing the film [15] in a glass petri dish containing 10ml of pH 6.8 phosphate buffer. The time required for the film to break & disintegrate was noted as in vitro disintegration test.

Drug content 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[16] was determined spectroscopically after appropriate dilution at 276 nm using UV visible spectrophotometer.

***In vitro* dissolution study:** Dissolution studies were performed in pH 6.8 phosphate buffer containing 900 ml at 37 ± 0.5°C, using USP type-II apparatus [17] with paddle rotating at 75 rpm containing buccal films. Aliquots of 5 ml were withdrawn at time intervals of 1, 2, 4, 6, 8, 10, 12 and 14 min were filtered and replaced with 5 ml of phosphate buffer pH 6.8. The samples were estimated for absorbencies of dissolved drug scanned at λmax 276 nm by using UV. The percentage cumulative drug release (% CDR) was calculated.

Accelerated Stability Study: Optimized medicated films were subjected to accelerated stability [18] testing as per ICH guidelines. Films were packed in USP type I glass vials with aluminium cap as a closure and kept in an incubator maintained at 40 ± 2°C and 75 ± 5% RH for 6 months. Changes in the appearance, residence time, release behavior and drug content of the stored bioadhesive films were investigated after 1, 2, 3, and 6 months. The data presented were the mean of three determinations.

RESULTS AND DISCUSSION

FTIR study

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.

Evaluation of solid dispersion

Micromeritic characterization of SD formulations

All the granules were evaluated for micromeritic properties (Table-3) such as angle of repose bulk density, tapped density, Carr's index and Hausner's ratio. All were found to be acceptable limits.

Physical characterization

All the granules were evaluated for physical characterization such as solubility, drug content, and %yield. It is shown in table 4.

***In vitro* dissolution study**

The *in vitro* drug release was carried out in phosphate buffer of pH 6.8. The % *in vitro* drug release from formulations SPF1, SPF2, SPF3 and SPF4 was found to be 90.81, 92.41, 95.37, and 97.73 % respectively at the end of 60 mins. The optimized formulation profile was given by SPF4 contained 1:4 as drug: carrier ratio (Fig. 4).Hence SPF4 was selected for buccal film incorporation.

Evaluation of buccal films

Thickness uniformity

All the films were evaluated for thickness by using thickness gauge with a least count of 0.01 mm. It was observed that the thickness of

all patch samples was found to be uniform in each formulation. It was reported in table 5.

Folding endurance

The folding endurance was determined as per the procedure mentioned in the methodology. It was found that all the formulations showed good folding endurance greater than 100. . It was depicted in table 5.

Surface pH

The surface pH of the patches was also determined and observed that the surface pH of each patch was found between 6.09 to 6.77 and which means that they may have less potential to irritate the buccal mucosa as a result patches will be compatible to mucosa. It was shown in table 5.

***In vitro* disintegration test**

Among the formulations prepared, it was observed in vitro disintegration time was found to be good to disintegrate. It is reported in table 5.

Drug content test

The percentage drug content of all formulations was found to be in the range of 95-99.5 %. It was acceptable. It is reported in table 5.

***In vitro* dissolution study**

The *in vitro* drug release was carried out in phosphate buffer of pH 6.8. The % *in vitro* drug release from formulations F1, F2, and F3 were found to be 88.57% (14 mins), 91.24% (14 mins), and 97.11% (4 mins), respectively. The optimized formulation F3 profile was was released within 4 mins because the polymer concentration was less. The dissolution profile was shown in figure 5

Stability studies

All the formulations were evaluated with respect to physical appearance, drug content, surface pH, swelling index and *in vitro* drug release. The results of stability studies of buccal films showed no significant change with respect to physical appearance, drug content, surface pH, and in vitro drug release at the end of 6 months. Buccal films were found to be physically and chemically stable.

CONCLUSION

The solubility was enhanced by preparing solid dispersion using carriers Pluronic F127. Solid dispersions were prepared using solvent evaporation method out of 4 formulations SPF4 was incorporated into buccal film. Buccal films were prepared using solvent casting technique. Out of 3, F3 formulation was optimised on drug release study, showing 97.11 % drug release within 4 mins. Hence this buccal film can be used for drug delivery giving more benefit to the patients.

REFERENCES

1. Barry BW,William AC. In: Swarbrick J(ed)) Boylon JC.Encyclopedia of pharmaceutical technology vol-II, Marcel Dekker: Inc New York. 1995; pp49-93
2. Sahoo CK, Nayak PK, Sarangi DK, Sahoo TK. A review on mucoadhesive drug delivery systems. International Journal of Universal Pharmacy and Bio Sciences 2013; 2(3):92-119
3. Habib F, Abdel Azeem M, Fetih G, Safwat M. Mucoadhesive buccal patches of lornoxicam. Bull. Pharm. Sci., 2010; 33(1):59-68.
4. Mahajan A, Chhabra N, Aggarwal G. Formulation and characterization of fast dissolving buccal films: A Review. Der Pharmacia Letter, 2011; 3(1):152-165.
5. Jithendra KP, Sudhir M, Prasad AR. formulation development and in-vitro evaluation of midazolam solid dispersions and their buccal flash disintegrating films. Panacea Journal of Pharmacy and Pharmaceutical Sciences 2015; 4(4): 801-816.
6. Fule R, Amin P. Development and evaluation of lafutidine solid dispersion via hot melt extrusion: Investigating drug polymer miscibility with advanced characterization. Asian J Pharm Sci 2014; 9:92-106.
7. Frizon F, Eloy JO, Donaduzzi CM, Mitsui ML, Marchetti JM. Dissolution rate enhancement of loratadine in polyvinylpyrrolidone K-30 solid dispersions by solvent methods. Powder Technol 2013; 235:532-9.
8. Zawar L, Bari S. Microwave induced solid dispersion as a novel technique for enhancing dissolution rate of repaglinide. Adv Pharmacol Pharm 2013; 1:95-101.
9. Lee SN, Poudel BK, Tran TH, Marasini N, Pradhan R, Lee YI, et al. A novel surface-attached carvedilol solid dispersion with enhanced solubility and dissolution. Arch Pharm Res 2013; 36:79-85.

10. Yan ZC, Jie DY. Genomic study of the absorption mechanism of cantharidin and its solid dispersion. Colloids Surf A Physicochem Eng Asp 2012; 415:295-301.
11. Aggarwal AK, Jain S. Physicochemical characterization and dissolution study of solid dispersions of ketoconazole with nicotinamide. Chem Pharm Bull 2011; 59:629-38.
12. Sahoo CK, Satyanarayana K, Ramana DV. Formulation and Evaluation of Solid Dispersion Containing Paracetamol. International Journal of Pharma And Chemical Research 2017;3(4):722-726.
13. El-Maghraby G. M., Abdelzaher M. M. Formulation and evaluation of simvastatin buccal film. J App Pharm Sci, 2015; 5 (04): 070-077.
14. Pandya P, Gattani S, Jain P, Khirwal L, Surana S. Co-solvent evaporation method for enhancement of solubility and dissolution rate of poorly aqueous soluble drug simvastatin: *In vitro - In vivo* evaluation. AAPS PharmSciTech, 2008; 9(4): 1247-1252.
15. Verma S, Kaul M, Rawat A, Saini S. An overview on buccal drug delivery system. International Jornal of Pharmaceutical Sciences and Research, 2011; 2 (6):1303-1321.
16. Rasool BKA, Khan SA. *In vitro* evaluation of miconazole buccal films. Int J Appl Pharm 2010; 2:23-6.
17. Rodaa A, Prabhub P, Dubey A. Design and evaluation of buccal patches containing combination of hydrochlorothiazide and atenolol. Int J App Pharm, 2018; 10(2): 2018, 105-112.
18. ICH harmonized tripartite guideline, Stability testing of new drug substance and product.Q1A (R2).Federal Register 2003; 68:65717-18.