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Research Article

Fabrication of Sublingual Alprazolam Wafers using Mucoadhesive *Vigna mungo* L. Seeds and Characterized with Texture Analyzer QTS-25

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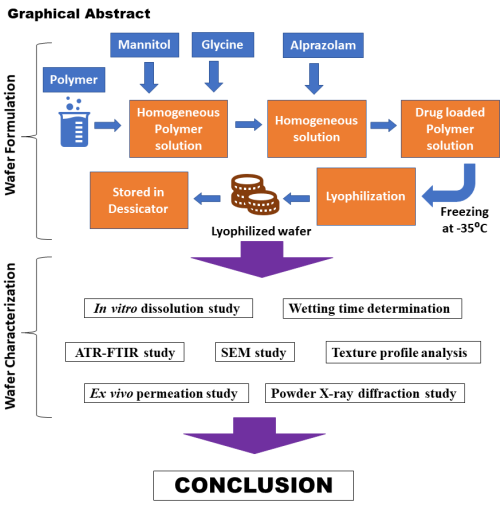
ABSTRACT

Our primary goal of this work was to create and test a mucoadhesive lyophilized rapid dissolving sublingual wafer of Alprazolam using a natural mucoadhesive agent extracted from black gram (*Vigna mungo L.*) seeds. We examined the pH, swelling volume, moisture absorption capability, mucoadhesive strength, and viscosity of the natural mucoadhesive agent. We compared it with synthetic mucoadhesive agents such as Hydroxypropyl cellulose (HPC) and Carbopol 934 (CP 934). The prepared wafers of both categories were characterized and compared for mechanical and texture properties, wetting time, disintegration time, Scanning Electron Microscopy (SEM), *in vitro* drug release, and *ex vivo* permeation study. We found that the pH of *V. mungo* mucilage (VMM) was 6.95±0.75, which lies between the normal sublingual mucosal range (pH 6-7), suggesting non-irritability to the mucosa. Attenuated total reflectance-Fourier-transform infrared (ATR-FTIR) peak showed no significant interaction between Alprazolam and mucoadhesive materials. The micrographs of SEM predicted good porosity of the wafer which leads to rapid wetting, disintegration, and dissolution. It is inferred from the study that the fast-dissolving wafer prepared from the VMM gave a better result than the HPC wafer in respect of various parameters. Hence, this study discovered an alternative method to deliver Alprazolam.



Keywords: Lyophilization; Permeability; Solid dosage form(s); Mucoadhesive; Texture

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INTRODUCTION

The transformation of an existing therapeutic molecule from a traditional form to a newer approach may substantially increase the safety, effectiveness, patient conformance, and reduce dose frequency. Oral fast-dissolving dosage forms (OFDDFs) are a comparatively new dosage technology that involves fast dissolution or disintegration of pharmaceutical formulations (tablet or capsule)[1–3] into a solution or suspension even without any liquid inside the mouth.[4,5] When the dosage forms come into touch with saliva, it begins to dissolve instantly. Within 30–50 seconds after delivery, the wafer disintegrates completely.[6]

Alprazolam (8-chloro-1-methyl-6-phenyl-4H-l,2,4, triazolo[4,3-α][1,4] benzodiazepine)[7], a central nervous system active compound, has clinical effectualness in treating Generalized Anxiety Disorder (GAD)[8] and used for the management of the panic disorder in presence or absence of phobic neurosis. For managing these disorders, rapid onset of drug action is desirable and achieved by parenteral administration of alprazolam, but this route is hazardous for various reasons. Alprazolam may penetrate across the sublingual mucous membrane[2,9,10] at biological pH (pH 7.4) as it is non-ionic and highly hydrophobic. Hence, the sublingual fast-dissolving wafer formulation of Alprazolam may replace the parenteral and conventional oral routes.

There are several techniques for manufacturing oral fast-dissolving dosage forms. The lyophilization method is one of the most convenient techniques to achieve these fast-dissolving wafers with sufficient structural integrity. Various types of wafers have been prepared over the years by different workers.

According to Mathews et al., lyophilized wafers administer medications to suppurate wounds.[11] They used xanthan gum (XG) and sodium alginate (SA) to make a set of wafers that were both augmented with methylcellulose (MC) of higher molar mass. Boateng et al. used sodium alginate (ALG) and sodium carboxy methyl cellulose (CMC) to make freeze-dried (lyophilized) wafers and solvent-cast films as prospective drug delivery methods for mucosal surfaces, including wounds.[12–14] They observed that solvent-evaporated films did not have the same substantial drug loading and water retention capacity as porous freeze-dried wafers containing paracetamol. Patel et al. created a lyophilized polymeric wafer matrix for fast oral mucosal drug delivery.[15] They asserted that lyophilization produced a porous matrix in the wafer that allowed simulated saliva (SS) to easily enter the hydrophilic structure. Mathews et al. made lyophilized wafers as topical medication delivery devices for the treatment of chronic wounds, offering a feasible alternative to gel suspensions.[16,17] He and his colleagues developed xanthan wafers comprising a selective, insoluble Metalloprotease-3 (MMP-3) inhibitor (UK-370,106) and a non-ionic surfactant, intending to deliver precise dosages of UK-370,106 to a suppurating wound site.

This study was aimed to create a sublingual Alprazolam wafer utilizing the lyophilization technique for quick oral mucosal drug administration, mainly to avoid G.I. adverse effects and produce a faster onset of action through the oral mucosal area. We have extracted the natural mucoadhesive agent from black gram seeds. We have used this mucoadhesive agent to prepare a wafer containing alprazolam.[18] We have also characterized them in terms of *in vitro* disintegration, *in vitro* drug release, drug-excipient compatibility study, *ex vivo* drug permeation study, etc. We prepared the formulation with a natural mucoadhesive agent compared with synthetic polymers Hydroxypropyl cellulose (HPC) and Carbopol 934 (CP 934).[19,20]

In this study, we have prepared a sublingual Alprazolam wafer using a natural mucoadhesive polymer (VMM) as a platform for the delivery of Alprazolam in the mouth to avoid first-pass metabolism and to get better therapeutic action and to overcome adverse effects (if any) caused by the synthetic polymers.

MATERIALS AND METHODS

Materials

Alprazolam was gifted by Burnett Pharmaceutical Pvt. Ltd. (Kolkata, India). Hydroxypropyl cellulose was gifted by Jubilant Life sciences Limited (Noida, India). Acetone and Carbopol 934 were purchased from Merck Limited (Mumbai, India) and S.D Fine Chem. Ltd. (Mumbai, India), respectively. Black gram seeds were purchased from the local market. Preformed blisters used for the manufacture of wafers were obtained from the empty blister pack of Digene® (Abbott Pharma Ltd.). We have purchased High-performance liquid chromatography (HPLC) grade Acetonitrile and water from Merck Specialties Pvt. Ltd. (Mumbai, India). All other materials used were of analytical quality.

METHODS

Mucilage extraction from Vigna mungo L. seeds

The seeds of *Vigna mungo* were washed twice with double distilled water. The mixture was then tripled in volume and heated in a water bath for four hours at 60°C. The resulting slurry was then filtered through muslin cloth and stored in the refrigerator overnight. The top supernatant was decanted and reduced the volume by heating it in a water bath at 60°C. After that, the extract was cooled to room temperature before mixing it with three times the amount of acetone. The separated masses were gathered and dried in an oven heated by hot air set to about 60°C. The dry portions were powdered and kept until needed.[14]

Characterization of isolated mucilage

Measurement of pH

The pH was measured at 25°C using 1% w/v aqueous solutions of isolated *V. mungo* mucilage (VMM) using a pH meter (Toshniwal Inst. Mfg. Pvt. Ltd. Ajmer, India).

Study of Swollen volume

We took about 1 gm of VMM and kept 20 mL of simulated saliva in a measuring cylinder. The swollen volumes of samples were observed after 24 h and calculated as follows:

$$Swollen\ volume = V_2 - V_1 \quad (1)$$

Where,

V_1 = Volume of the mucoadhesive agent before swelling

V_2 = Volume of the mucoadhesive agent after swelling

Viscosity determination

Using a TV-10 Viscometer (Toki Sangyo Co. Ltd., Japan) with spindle M1 and cord No. 20, the viscosity of a 1 percent weight-per-volume aqueous solution of VMM was measured at four different speeds of 10, 30, 60, and 100 rpm, respectively at 25°C.

Moisture sorption capacity

About 2g of VMM sample was accurately weighed and uniformly dispersed on a Petri dish's surface. After that, the sample was placed in a humidity chamber (Electrolab, India) with a relative humidity of 99% and a temperature of 25°C. At the end of 72 hours, the exposed sample gained weight[21] which was noted, and the following equation was used to determine moisture sorption capacity:

$$Moisture\ sorption\ capacity\ (\%) = \frac{M_2 - M_1}{M_1} \times 100 \quad (2)$$

Where,

M_1 = Initial mass of sample (g)

M_2= Mass of the sample after absorbing moisture (g)

Measurement of mucoadhesive strength using texture analyzer

The mucoadhesive strength of VMM was examined by QTS-25 Texture Analyzer (Brookfield Engineering Labs., Inc., USA) utilizing recently harvested goat sublingual mucosa.[22,23] The newly dissected goat mucosal membrane was affixed to the instrument's top probe and dropped onto the surface of another mucosa at a constant velocity of 10^{-3} m/s and constant force of 0.1 N, with a drop of 1% w/v aqueous mucilage in between them. After a contact time of 5, 10, 15, 20, and 30 min, respectively, the probe was moved vertically upwards at the same speed. The mucoadhesive materials and membrane needed to be in close contact.[24] Therefore, the bio adhesive force was assessed at 37±0.5°C. The mucus membrane's exposed surface measured 1.14×10^{-4} m^2.

All the measurements mentioned above were carried out for synthetic mucoadhesive substances like HPC and Carbopol 934 and compared with the natural ones.

Preparation of fast-dissolving wafer

Fast-dissolving sublingual wafers were formulated as per the composition ratio of Table 1. De-ionized water was used to dissolve the ingredients, and stirring was done for half an hour. The clear mixture was drawn and put in the correct amount into polystyrene moulds that had been pre-lubricated. The formulation was frozen for 2 hours at -60°C in a freeze-dryer. The drying process lasted for 72 hours at a pressure of 10-15 m torr. Wafers were preserved in glass containers free from moisture. The flowchart for the preparation of the wafer is shown in Figure 1.

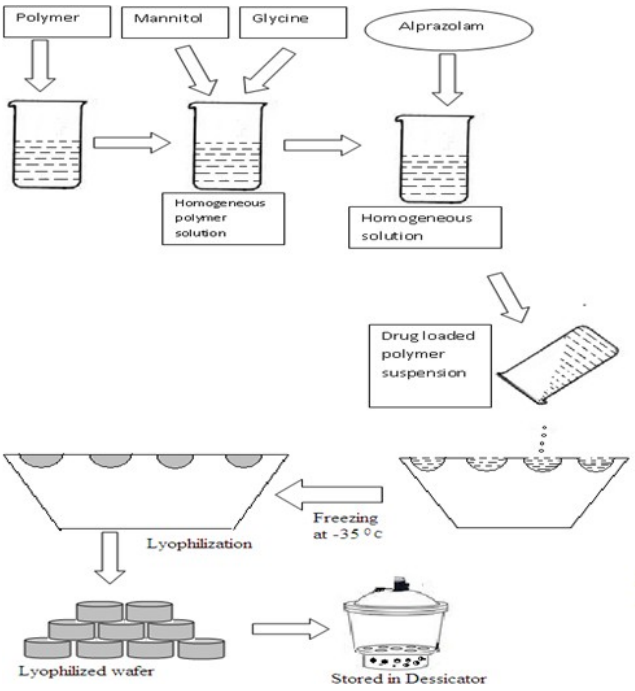

Fig. 1: Flow chart of wafer preparation method

Characterization of fast-dissolving wafers

Visual inspection of wafers

Freeze-dried wafers were evaluated for various morphological characters, comprising shape, colour, surface structure, and durability. The wafers were also evaluated for their adhesion to the blister pack and the easiness of taking them out.

Table 1: Formulation of Alprazolam wafers

Formulation Code	HPC1	HPC2	HPC3	HPC4	VMM1	VMM2	VMM3	VMM4
Alprazolam (mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HPC (%w/v)	1.0	2.5	5.0	10.0	-	-	-	-
VMM (%w/v)	-	-	-	-	1.0	2.5	5.0	10.0
Mannitol (%w/v)	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Glycine (%w/v)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Mechanical properties and Texture profile analysis

Mechanical properties (hardness, fracture force) and texture properties (matrix energy absorbed, tolerance value, yield value, and resilience) of the prepared wafers were evaluated using QTS-25 Texture Analyzer (Figure 2). At a speed of 5 mm/min, an analytical probe of diameter 1.2mm compressed the wafer to a depth of exactly 2mm. A trigger force of 5 kg was applied.[23] Once the measurement was complete, the data were stored and plotted using the Texture Pro Software version 2.1. Figure 3 depicts the typical force-distance and force-time curve useful to determine the parameters mentioned above as follows:

Matrix energy absorbed= Area Under the Curve (AUC) between marker 1 and marker 3 of the force-distance curve.

Matrix yield value= Gradient between marker 1 and marker 2 of the force-distance curve.

Matrix tolerance value= Gradient between marker 1 and marker 3 of the force-time curve.

Matrix Resilience value =

$$\frac{AUC\ between\ marker\ 2\ and\ marker\ 3\ of\ force-time\ curve}{AUC\ between\ marker\ 1\ and\ marker\ 2\ of\ force-time\ curve} \text{———-(3)}$$

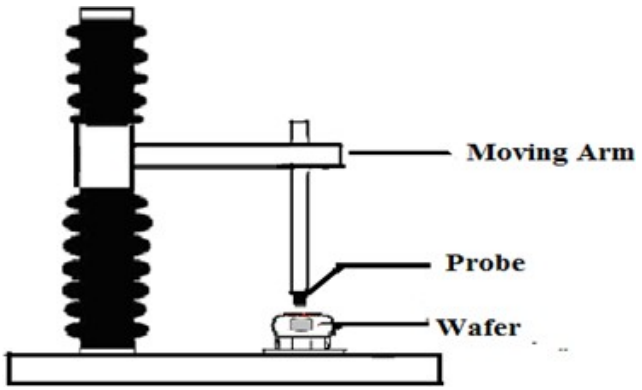

Fig. 2: Determination of hardness and fracture force by Texture Analyzer

Wetting time

In a Petri dish (internal diameter 10 mm) containing 10 ml of simulated saliva with eosin, a water-soluble stain, a piece of tissue paper folded twice was retained. The wafers were cautiously placed in the centre of the Petri dish, and the amount of time it took for the colour to reach the upper surface of the wafer was noted as the wetting time. (Figure 4).

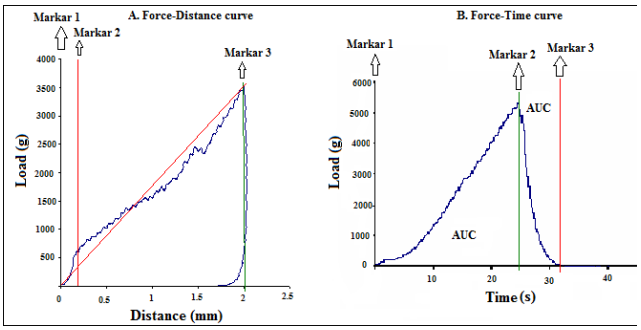

Fig. 3: Texture profile analysis

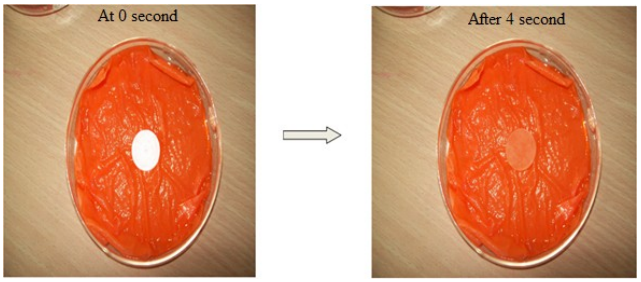

Fig. 4: Determination of wetting time

ATR-FTIR study

The ATR-FTIR spectrum of Alprazolam, mucoadhesive agents, and mixtures of Alprazolam with mucoadhesive agents were recorded to check incompatibility between drug and excipients if any. The slip-clutch mechanism was used to apply maximum pressure to the samples over the attenuated total reflectance (ATR) crystal. With a 1-minute sample and 1-minute background collection durations, all spectra were acquired at 4 cm^{-1} spectral resolution. ATR-FTIR spectrophotometer (Bruker Optics Inc, USA) was used to record spectra in the range of 4000 cm^{-1} to 400 cm^{-1}.

SEM study

The surface topography of the optimized wafer formulations was done by using JSM-6360 (JEOL Ltd, Tokyo, Japan) Scanning Electron Microscope. Prior to the examination, the cross-section of the wafers was gold sputtered to render electrically conductive.

Powder X-ray diffraction (PXRD)

For the X-RD peak of the optimized wafer formulations, Rigaku Analytical X-ray powder diffraction (XRD) (Miniflex, Tokyo, Japan) was employed to examine the crystalline properties of alprazolam. Powder samples were checked between diffraction angles 2θ of 5^o and 40^o. Crystallinity was determined by comparing a few typical peak heights in the diffraction patterns of the wafers and those of Alprazolam powder. The relative degree of crystallinity (RDC) was determined by the formula:

$$RDC = \frac{H_{sample}}{H_{drug}} \quad \ldots\ldots\ldots (4)$$

Where H_{sample} is the peak height of the wafers under observation and H_{drug} is the peak height at the same angle for the drug.[25]

Disintegration time measurement

For *in vitro* disintegration of the fast-dissolving sublingual wafer, a novel modified disintegration method was developed as there is no standard official method. The wafers were placed carefully at the centre of the Petri dish containing simulated salivary fluid (pH 6.8) and the time for complete disintegration of the wafer was noted using a digital stopwatch. To achieve the highest level of precision, only one wafer was examined at a time.

Drug release studies from alprazolam wafers

In vitro release of Alprazolam from wafers was examined with a modified dissolution apparatus (Figure 5), consisting of a jacketed vertical glass beaker (i.e., a small beaker inside a large beaker), containing 100ml of simulated saliva[26] (pH 6.8) at 37^oC. A slow stirring of 50 rpm was applied using a magnetic stirrer. At predetermined intervals, 2mL of the sample was taken out and replaced with fresh simulated saliva. After proper dilution samples were impregnated through a 0.45μm membrane filter and then tested for drug release using a Jasco V-550 UV/VisSpectrophotometer (Tokyo, at λ_{max} of 222 nm), using simulated saliva as the blank.

Drug permeation using Franz diffusion cell

Franz diffusion cell (Figure 6) with 100mL simulated saliva was used to conduct *ex vivo* permeation of the drug from the optimized formulation. The Franz diffusion cell remained at a constant temperature of 37 ± 1^oC throughout the investigation. A freshly cut goat sublingual mucosa with adiffusion surface of 2.54 cm^2 was installed at the bottom of a compartment,[22,23] and formulations were poured into it. To keep the constant internal, environment, 1 mL of sample was taken out at predefined intervals and replaced with an equivalent volume of freshly prepared simulated saliva that had been pre-warmed to (37 ± 1^oC). The samples were then diluted to the proper concentration and measured at 222 nm using a Jasco V-550 UV/VIS Spectrophotometer (Tokyo, Japan).

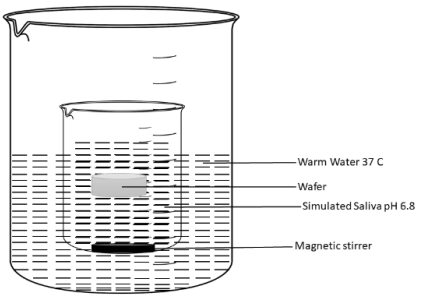

Fig. 5: Modified dissolution apparatus used for dissolution study of wafer

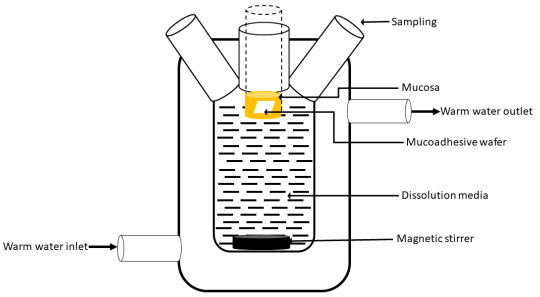

Fig. 6: Schematic representations of Franz-Diffusion cells used for *ex vivo* permeation study

RESULT AND DISCUSSION

Characterization of isolated natural mucoadhesive agents

Table 2 depicts the pH, swollen volumes, and moisture sorption capacity of mucoadhesive agents. The pH of a 1 percent weight-per-volume aqueous solution containing VMM, HPC, and CP 934 was approximately equal to sublingual pH (pH 6-7), suggesting their non-irritability and biocompatibility with sublingual mucosa. Hence the natural mucoadhesive agent can be effectively used in the preparation of fast-dissolving sublingual wafers.[27]

The capacity of mucoadhesive polymers to swell is an essential characteristic. For a polymer to be bio-adhesive, it must have a specific degree of swelling. However, excessive swelling caused by excessive hydration results in the creation of a slick surface, which reduces bio adhesion. In Table 2 VMM exhibits slightly higher swelling volume than HPC but significantly lowers than that of CP 934.

Table 2: Values of pH, swollen volume, and moisture absorption capacity

Polymers	pH at 25°C	Swollen volume (ml)	Percent moisture sorption capacity
VMM	6.95±0.75	9.5±0.75	13.35±1.42
CP 934	2.56±0.95	19.5±1.90	10.80±1.65
HPC	4.25±0.75	9.0±0.85	15.84±1.21

Figure 7 shows the plot of viscosities of 1 percent weight-per-volume aqueous solution of VMM, HPC, and CP 934. It is in the range of 13.41-43.32, 12.14-41.55, and 14.37-44.34 mPa respectively. It is found that the viscosity of VMM at the same concentration of synthetic polymer is almost similar. So VMM may be considered a natural mucoadhesive agent for fast-dissolving sublingual wafers. It was found that the moisture absorption value is not so high which indicates lesser susceptibility to microbial growth.

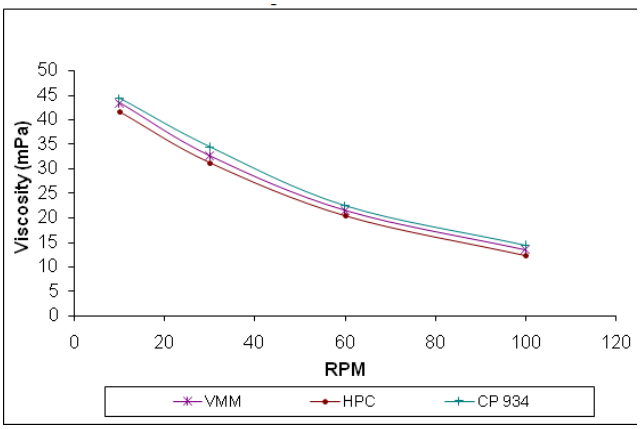

Fig. 7: Comparative viscosities of different mucoadhesive agents at different RPM

Mucoadhesive strength mainly depends on the interaction of the polymer with the mucin molecule and contact time.[28] Figure 8 depicts the comparative mucoadhesive strength of the natural and synthetic mucoadhesive agents. It is observed that mucoadhesive strength is increased with a simultaneous increase in contact time and concentration of mucoadhesive agents. VMM showed better mucoadhesive strength than the synthetic polymers.

ATR-FTIR study

Figure 9 represents the ATR-FTIR spectra of Alprazolam alone as well as individual excipients and a combination of drug-excipient mixtures. It is observed that slight changes of the parent peak in the case of the drug-excipient mixture have occurred that may be due to the formation of hydrogen bonding, indicating no significant interaction between the drug and excipient mixture.

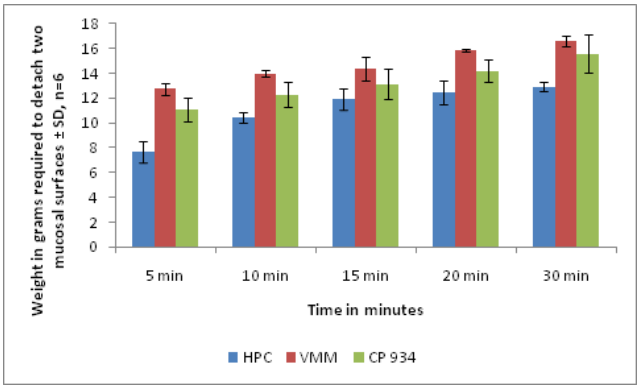

Fig. 8: Using the Texture Analyzer, comparative bio adhesive strength of 1 percent w/v watery slurry of several mucoadhesive agents.

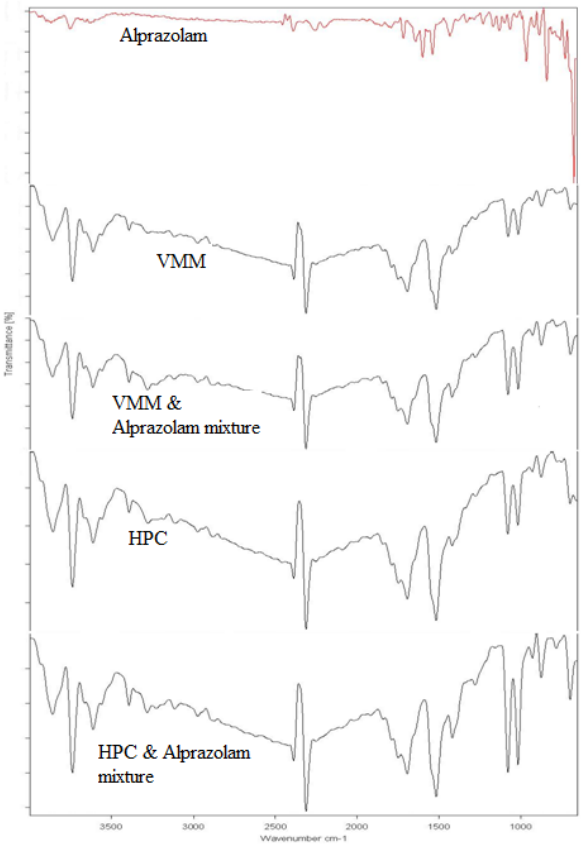

Fig. 9: Comparative ATR-FTIR study of Alprazolam alone, mucoadhesive agent and their mixture

Characterization of fast-dissolving wafers

All the wafer formulations produced dry and exquisite wafers that could withstand physical handling. The wafers were visually characterized for their morphological properties and Table 3 depicts the results. The results indicated that, at lower polymer concentrations, the surface of the wafers was relatively porous and sometimes very fragile in nature. But as there was an increase in polymer concentration, the surfaces of wafers became rigid and durable. Generally, wafers were easily removed from the blister well but an increase in polymer concentration resulted in difficulty of removal from the blister well. The thickness and diameter of all the wafers were within the acceptable limit irrespective of polymer concentration.

Table 3: Visual inspection, thickness and diameter of the wafers (n=6)

Formulation No.	Surface of tablet	Durability	Removal from the tablet	Thickness (mm±SD)	Diameter (mm ±SD)
HPC1	Porous brittle	Fragile	+	5.05±0.65	22.65±1.56
HPC2	Porous, burst	Durable	+	5.67±0.45	22.55±1.2
HPC3	Porous, smooth	Durable	++	5.76±0.15	22.56±2.3
HPC4	Porous, rigid	Stable, hard	+++	5.43±0.22	22.54±1.5
VMM1	Porous, smooth	Durable	++	5.65±0.5	22.77±2.98
VMM2	Porous, smooth	Durable	+++	5.72±0.25	22.76±1.0
VMM3	Rigid, smooth	Durable	+++	5.11±0.13	22.62±1.1
VMM4	Rigid, smooth	Stable, hard	+++	5.32±0.55	22.65±1.2

(+) difficulty in removal, (++) moderately removed, (+++) easily removed

SEM study

Figure 10 (A-D) displays SEM images of the face and transverse-section views of HPC3 and VMM1 wafers. The micrographs revealed the very porous character of the lyophilized wafers, indicating fast water penetration and subsequent wetting, disintegration, and dissolution of the wafers in the mouth. SEM patterns revealed that VMM1 wafers have bigger and more diffused holes than HPC3 wafers, which might explain the HPC3 wafers' quick *in vitro* disintegration and short wetting time.

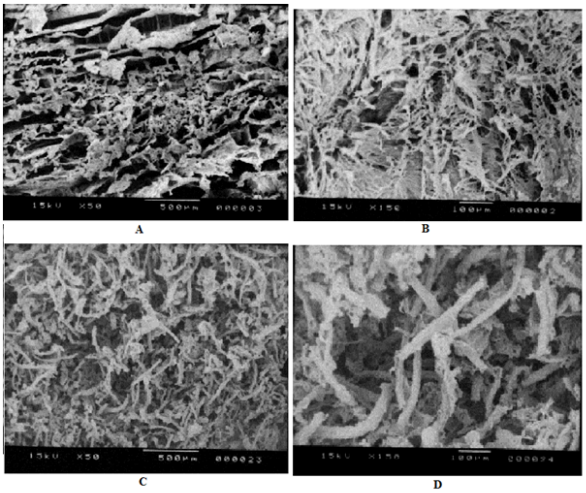

Fig. 10: Typical scanning electron microphotograph of (A) VMM1 at 50× zoom, (B) VMM1 at 150× zoom, (C) HPC3 at 50× zoom and (D) HPC3 at 150× zoom

Powder X-ray diffraction study

The crystalline structure of alprazolam is demonstrated by a powerful and distinctive x-ray diffraction peak. Despite the presence of multiple scattering lines in the powder pattern, the pattern is dominated by powerful scattering peaks situated at 9.41°, 12.05°, 14.81°, 18.26°, 18.98°, 19.94°, 24.11° and 26.33°2θ. The absence of widening and decrease of key Alprazolam diffraction peaks in the HPC3 and VMM1 wafers' diffraction patterns indicated that the wafers were mainly amorphous (Figure 11). The RDC was calculated using the drug peak at 24.11°2θ. For HPC3 and VMM1 wafers, the computed RDC values were 0.36 and 0.42, respectively. From this study it is evident that aqueous solubility of Alprazolam has increased because of lowering of strong crystal lattice structure that improved aqueous solubility of drug.

Mechanical strength of wafer matrix

The mechanical strength (hardness and fracture force) of the wafer is represented in Table 4. The data showed that the hardness and fracture force of the wafers progressively decreased with a decrease in polymer concentration. An increase in hardness ultimately results in an increase in the rate of hydration and eventual dissolution which is not desirable for the fast-dissolving dosage form. An optimum hardness thus is required for the proper functioning of the fast-dissolving dosage form. It has been predicted that hardness greater than 30N results in optimum mechanical strength.

Table 5: The texture properties of wafer matrix

Formulation code	Energy of absorption (Joule)	Matrix yield value (N/mm)	Matrix tolerance value (N/mm)	Matrix resilience (%)
HPC1	0.0025±0.0001	0.0226±0.005	0.2115±0.005	8.431±0.85
HPC2	0.0042±0.0005	0.0526±0.008	0.6317±0.009	10.013±0.65
HPC3	0.0285±0.003	0.1458±0.096	1.1850±0.75	12.891±0.45
HPC4	0.1631±0.065	0.8420±0.015	2.7735±0.95	16.540±1.25
VMM1	0.0209±0.0045	0.6092±0.085	1.0611±0.54	10.663±2.35
VMM2	0.0419±0.0085	0.7367±0.015	1.3265±0.73	13.511±2.56
VMM3	0.1643±0.075	0.9977±0.065	1.6380±0.45	15.517±3.54
VMM4	0.2581±0.015	1.2125±0.85	2.5430±0.65	18.215±2.65

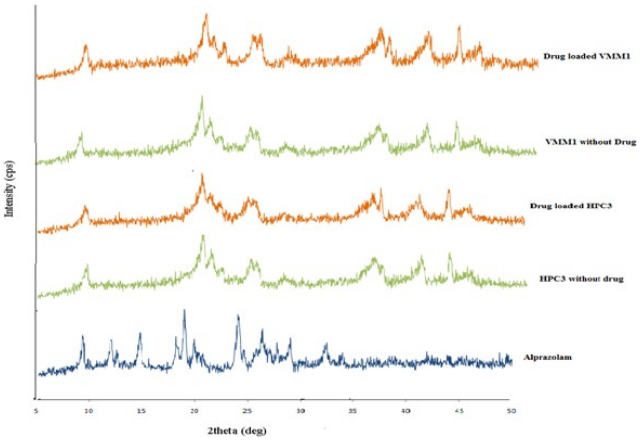

Fig. 11: Comparative powder X-ray diffraction study

Table 4: The mechanical strength in terms of hardness and fracture force of the wafers

Formulation code	Hardness (N)	Fracture force (N)
HPC1	14.25±2.4	10.45±3.45
HPC2	20.49±2.15	17.84±1.5
HPC3	34.57±1.2	29.63±1.8
HPC4	246.71±25.5	41.29±1.5
VMM1	32.76±2.12	27.56±1.95
VMM2	39.47±2.22	30.67±2.12
VMM3	56.58±7.75	41.64±2.15
VMM4	75.65±12.54	54.32±1.85

Texture profile analysis

Table 5 explained the Textural Profile Analysis (TPA) of the wafer lattice. Higher values indicatestronger wafer grids. The absorbed matrix energy was utilized to compute the wafer integral structural performance between the wafer surface and the interconnected polymer frameworks created during lyophilization.[29] Because the gaps within the wafer matrix enabled energy to be trapped, higher energy absorption was seen as the polymer concentration increased. The matrix tolerability and decomposition rate, and matrix fracturability of the wafer were all affected by the low polymer content. Due to the wafer's initial energy, less effort was needed to crack the wafer. The porosity of wafers is shown by matrix resilience. Wafer porosity is essential for achieving a quick breakdown of the wafer system in the sublingual cavity. However, a wafer matrix with extreme porosity may have huge apertures and holes, which can reduce lattice aggregation and cause poor robustness. VMM1 and HPC3 wafers may be considered the best formulations in this study.

Disintegration time and wetting time

Disintegration and wetting time from the wafers are represented in Table 6. The results showed that both parameters increase with the increase of polymer concentration. Neither the European Union nor the United States Pharmacopoeia has defined disintegration tests for fast-dissolving tablets. An ideal time of breakdown of mouth-dissolved tablets is half minute or less,[30] according to literature. Experiments have revealed that *in vitro* disintegration periods can be much longer or shorter than *in vivo* disintegration times.[31]

Table 6: The disintegration and wetting time of the wafers

Formulation code	Disintegration time (sec)	Wetting time (sec)
HPC1	2.30±0.45	1.65±0.75
HPC2	3.01±0.95	2.56±0.15
HPC3	6.58±0.45	4.65±0.54
HPC4	37.18±1.25	23.65±1.25
VMM1	6.12±0.25	3.56±0.55
VMM2	14.90±1.5	10.95±0.95
VMM3	33.49±2.1	27.85±2.85
VMM4	60.65±1.45	45.85±3.1

The wafer matrix disintegration was used to evaluate the speed at which the wafer broke down and thus released the medicament. The wafers having sufficient hardness (greater than 30 N), fracture force (greater than 20N), and a relatively short disintegration time (less than 10s) weare designated as optimum for this study. HPC3 and VMM1 showed the optimum results.

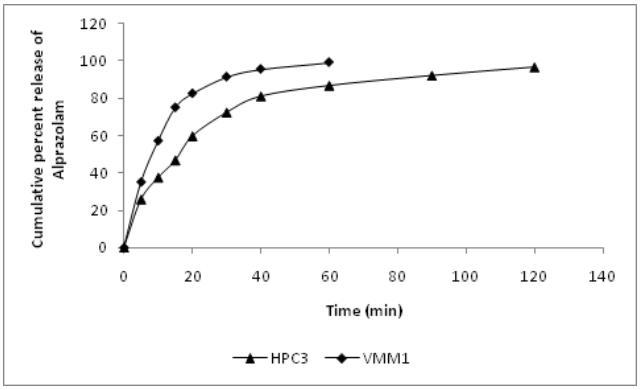

Fig. 13: Comparative *ex vivo* permeation study of HPC3 and VMM1 wafers

In vitro dissolution study

In vitro drug release from the different wafer formulations are shown in Figure 12. It is found that 99% drug release occurred within 60 min in case of VMM1 but it took 90 min in case of HPC3. The rate of dissolution reduces as polymer content rises, which may be related to these formulations increased mechanical strength, which affects both their rate of hydration and final dissolution. This has an impact on how quickly the medication diffuses through the gel and is released into the dissolving media. The kind and amount of polymer,[32] the percentage and grade of the polymer,[33] and polymer hydration properties[34] have all been proven to have an impact on the mechanism of drug release, as well as the tempo and extent of drug release. As the polymer concentration rises, the rate of drug release from the wafers rises as well.

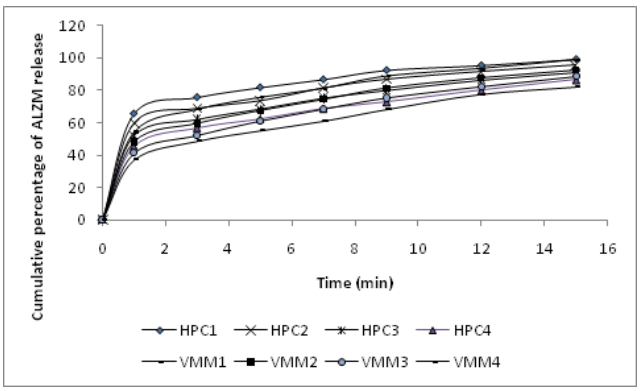

Fig. 12: *In vitro* drug release from the wafer formulations

Study of Ex vivo permeation

HPC3 and VMM1 wafers with improved formulations were investigated for *ex vivo* Alprazolam permeation, and the findings are shown in Figure 13. The $t_{85\%}$ was found to be 55.76±2.54 and 22.6434±1.55 min respectively, suggesting VMM1 is permeated better through the membrane than HPC3 wafer.

CONCLUSION

The findings in respect of the physical properties of Alprazolam wafers, *ex vivo* drug permeation, and, *in vitro* drug release, showed that the wafer formulation created in this study might be a viable alternative to traditional Alprazolam formulations. This research also revealed that natural mucoadhesive agents performed better than synthetic polymers.

In this study, the prepared sublingual Alprazolam wafer using a natural mucoadhesive polymer (VMM) suggested as an alternative platform for the delivery of Alprazolam in the mouth to avoid first-pass metabolism and better therapeutic performance.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Not Applicable.

AUTHOR CONTRIBUTIONS

KAA: Writing, Reviewing and Editing; SC: Writing, Visualization, Illustrative diagrams, and editing.

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