doi.org/10.36721/PJPS.2023.36.5.SP.1649-1656.1

Biopolymer based film loaded with Cholecalciferol: A novel technique to enhance nutritional supplement absorbance

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Abstract: In terms of delivery systems for active compounds, orally disintegrating films are a great option. The initial stage in creating an oral disintegrating film is selecting a film-forming polymer. The basic polymers combination Microcrystalline Cellulose (MCC), which is co-processed with Carboxymethylcellulose Sodium (CMC) and hydroxypropylmethyl cellulose were used to create an oral disintegrating film that contains cholecalciferol (Vitamin D3), a fat-soluble vitamin that aids in the body's absorption of calcium and phosphorus. The goal of the current inquiry was to develop orally disintegrating films of vitamin D3 to improve patient comfort and compliance for pediatric or elderly patients due to its simplicity of administration. Films containing drugs and made of the appropriate plasticizer and chosen polymers demonstrated outstanding film forming and folding endurance. The dissolution test showed that Vitamin D3 has a rapid disintegration property, with the majority of it dissolving in the medium (pH 6.8) in less than two minutes after being inserted. To verify that the films were successfully formed, a variety of procedures including HPLC, FT-IR and microscopic studies were employed. When kept at 40^{o}C with humidity of 75%, the film showed good stability for at least three months.

Keywords: Film, folding endurance, dissolution, oral, casting.

INTRODUCTION

For patients with dysphagia or aphagia, oral jerry preparations and oral disintegrating tablets (ODT) have been created (Nishimura *et al*., 2009; Shimoda *et al*., 2009). ODT are easily dissolved and can be taken with little to no water, but the dissolved components are insoluble and must be swallowed (Gopinath *et al*., 2013). The tablet preparations have the benefit of being ingested without choking and are beneficial for older patients, but they are frequently large. In order to prevent breakage during transit, the orally disintegrating tablets are also produced at a higher crushing strength. Even with a higher concentration of superdisintegrants, the increase in hardness compromises the rate of disintegration (Sharma *et al*., 2016). In contrast, edible thin film compositions have been employed as oral care items to treat different diseases. These medications dissolve in the saliva, therefore drinking water is not necessary to take them. The fat-soluble secosteroid vitamin D3 is use to improving the absorption of calcium, iron, magnesium, phosphate and zinc through the intestinal wall. Adult men with impotence also referred to as erectile dysfunction, can benefit from taking vitamin D3 (Rafeeq *et al*., 2020). To get immediate results in this study, we created Vitamin D3 Oral films, which are tiny films that rapidly dissolve into the buccal cavity. This movie may use many flavors and viewers may select from a number of flavors. These oral films containing active vitamin D3 have a strawberry flavor. Any of the numerous water soluble polymers, including maltodextrin, HPMC and (MCC+CMC) can serve as the basis material for vitamin D3 oral films.

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MATERIALS AND METHOD

Chemicals

HPMC E5 was obtained from Colorcon Ltd. Maltodextrin and PEG 6000 was donated for our research by Daejung Chemicals and Metals Siheung-si, South Korea. Saffron Pharm in Faisalabad, Pakistan, supplied 99% pure Vitamin D3 and (MCC+CMC) for research objectives.

Synthesis

The two polymers were used to create drug-loaded films using the solvent casting technique. At a dosage of 5 mg per 4 cm^2 film area, vitamin D3 was added. In order to create films with the necessary thickness when cast on the calculated total surface area of the Petri plate, the amount of drug put into the film forming solution was calculated by taking into account the total amount of solution that

must be poured. Weighed amounts of the plasticizer (PEG 6000) and polymer (HPMC E5 1g and (MCC+CMC) were added to 20 mL of water, mixed until the polymer was dissolved and then set aside to release any trapped air. Maltodextrin and vitamin D3 were added to 5 mL of ethanol while being stirred at a speed of 1000 rpm. The two solutions were then thoroughly combined before being sonicated to remove air. A few drops of the flavoring ingredient were applied at the end. On a plastic petri dish, film was cast and it dried entirely at 40°C. Peeling off the dried films was followed by storing them in airtight containers in a dry environment until they were picked up for further analysis.

Physical characterization

The thickness of the polymeric composite films was measured with an accuracy of ±0.001 mm using a digital vernier caliper (Roy & Rhim, 2020). Film weight variation was calculated by weighing five randomly selected samples (n= 3)(4cm^2) using an electronic weighing scale (OHAUS adventurer Analytical balance, USA) (Patel *et al*., 2018) The folding strength of a hydrogel film was measured by counting the number of times a sample could be folded without developing cracks or breaking. We manually tested the films' folding endurance by folding them over and over again in the same location. All parameter results were shown as mean ±SD (Thakur *et al*., 2016).

Determination of drug entrapment efficiency

Drug entrapment efficiency was evaluated by slicing vitamin D film into 4cm^2 and dissolve into 10mL of solvent (30mL of ethanol and 70mL freshly prepared pH 7.4 phosphate buffer USP). Sonication was used to remove the vitamin D within just 5 minutes. Vitamin D amount was measured in a solution using an HPLC detector set to a maximum wavelength of 265 nm (Barkat *et al*., 2017; Korany *et al*., 2014). Following equation has been used to evaluate the entrapment effectiveness of the prepared film for vitamin D (Anwar *et al*., 2020).

$$\text{Entrapment efficiency \%} = \frac{\text{Actual drug content in film}}{\text{Theoretical drug content in film}} \times 100 \quad (1)$$

Optical microscopy

The film surface morphology was investigated using SEM JEOL analytical electron microscope. On an aluminum mount, a cut-out film sample was sputtered through gold and palladium (Dutta *et al*., 2016). The atomic force microscope is recently the most often used scanning probe microscope for roughness of film. The instrument was operated in a laboratory controlled to 25±2°C and 45±10% relative humidity.

Fourier transform infrared spectroscopy

It is a method for figuring out the structural relationships between pure components and the functional groups. To identify the functional group and interaction, tests were conducted on vitamin D, loaded fil, HPMC E5 and (MCC+CMC). Using a Bruker FTIR (Tensor 27 Series - Bruker Corporation Germany) equipment and attenuated-total-reflectance (ATR) technology, the value range of 4,000 to 800 cm-1 for spectrum scans has been obtained (Acharjya *et al*., 2010; Kamoun, 2016; Mehmood *et al*., 2020b).

Release study

Drug release was examined using the USP Dissolution Apparatus II at a basic pH of 6.8. In order to maintain a constant drug concentration inside the dissolving medium, the weighted film was added to 900 mL of the dissolution liquid (water) and spun continuously at 50 rpm. The dissolving medium was set to a temperature of 37°C. Samples were taken every 1, 3, 5 and 10 minutes as per the schedule. The sampled volume was consistently replaced with a new medium. HPLC was used to determine the maximum vitamin D release at 265 nm (Malik *et al*., 2017). Following formula was used to determine the percentage release.

$$\text{\% Release} = \frac{\text{Absorbance of the sample solution}}{\text{Absorbance of the standard solution}} \times 100 \quad (2)$$

Hemolytic investigations

To perform the hemolytic test on human blood, the precipitate was placed in a tube containing ethylene diamine tetra-acetic and spun at 1500 rpm for 5 minutes. The supernatant was then removed and the precipitate was then rinsed three times with phosphate buffer saline (PBS). It is necessary to combine 4 mL of phosphate buffer saline with 200mL of washed blood sediment before vortexing the mixture for a while. After the samples were maintained at 37°C for 5 hours, the mixture was centrifuged at 1500 rpm for 5 minutes. Calculate the supernatant's absorbance at 541 nm. Triton X-100 served as the positive control in this experiment, whereas phosphate buffer saline served as the negative control. In blood cells, hemolysis was observed under a microscope and it was calculated using Equation (3) (Wang *et al*., 2021).

$$\text{\% Hemolysis} = \frac{\text{ABS sample} - \text{ABS blank}}{\text{ABS positive} - \text{ABS blank}} \times 100 \quad (3)$$

In situ disintegration time

A volunteer who was asked to rate the film's bitterness underwent *in vivo* disintegration. After rinsing, one film was placed in the middle of the tongue and the time it took for it to completely degrade was noted. The degraded material was then retained in the mouth for an additional 60 seconds before being spit out. Distilled water was used to completely rinse the mouth.

Finally, bitterness was measured based on its level of intensity. The institutional ethics committee, the Declaration of Helsinki's founding ethical principles and the regulatory standards for good laboratory practice (GLP) were all followed in the conduct of the human experiment (Yan *et al*., 2010).

Table 1: Composition of formulation

Formulation Code	HPMC (g)	Necoel (mg)	PEG(mg)	Maltodextrin.(mg)	Vitamin D (mg)
VF-1	1.0	100	50	20	100
VF-2	1.0	200	50	20	100
VF-3	1.0	300	50	20	100
VF-4	1.0	400	50	20	100
VF-5	1.0	500	50	20	100

Table 2: Drug entrapment efficiency (all formulations)

Code	Drug Entrapment Efficiency
VF-1	57.23
VF-2	62.82
VF-3	73.91
VF-4	81.32
VF-5	98.91

Table 3: Results of Physicochemical evaluation of film (n = 3).

Formulation	Thickness(mm)	Weight variation (g)	Folding Endurance	Moisture content %	Moisture uptake %
VF-1	0.038 ± 0.22	0.442 ± 0.67	440 ± 11	10.20 ± 1.42	12.10 ± 1.71
VF-2	0.041 ± 0.13	0.481 ± 0.23	423 ± 19	09.70 ± 1.23	12.60 ± 1.32
VF-3	0.059 ± 0.25	0.592 ± 0.12	480 ± 11	11.20 ± 1.34	13.30 ± 1.45
VF-4	0.069 ± 0.03	0.692 ± 0.23	490 ± 17	12.10 ± 1.16	15.12 ± 1.42
VF-5	0.075 ± 0.14	0.616 ± 0.22	450 ± 12	11.80 ± 1.27	13.70 ± 1.25

Table 4: Results of Physicochemical parameters of film after stability period.

Formulation (Month)	Thickness(mm)	Weight variation (g)	Folding Endurance	Moisture content %	Moisture uptake %
VF-5 (0)	0.058 ± 0.34	0.566 ± 0.12	539 ± 32	17.23 ± 1.37	19.27 ± 1.23
VF-5 (3)	0.058 ± 0.34	0.566 ± 0.12	539 ± 32	17.23 ± 1.37	19.27 ± 1.23

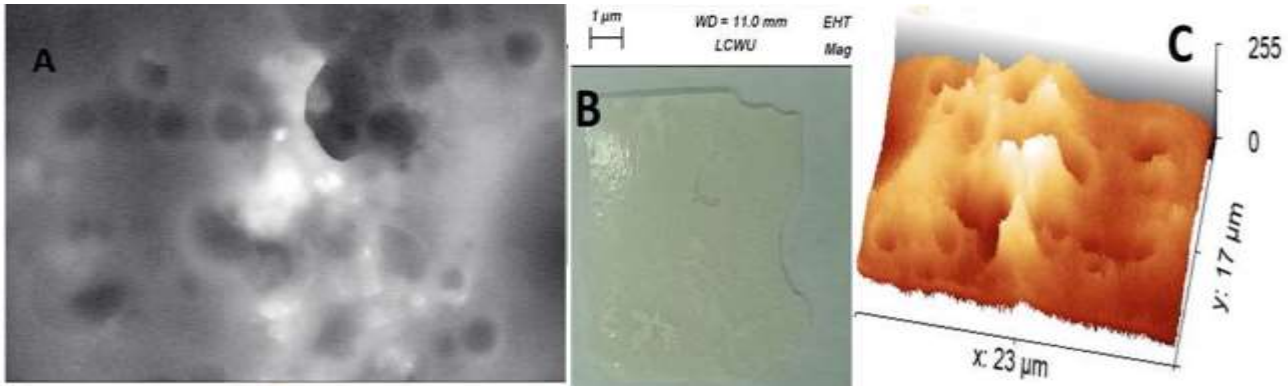

Fig. 1: SEM and AFM images of film

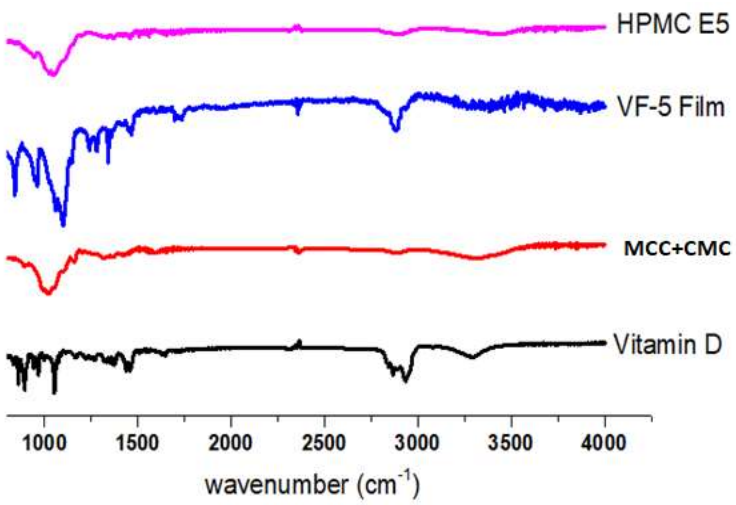

Fig. 2: FTIR spectra of (MCC+CMC), HPMC E5, Vitamin D and film (VF-5)

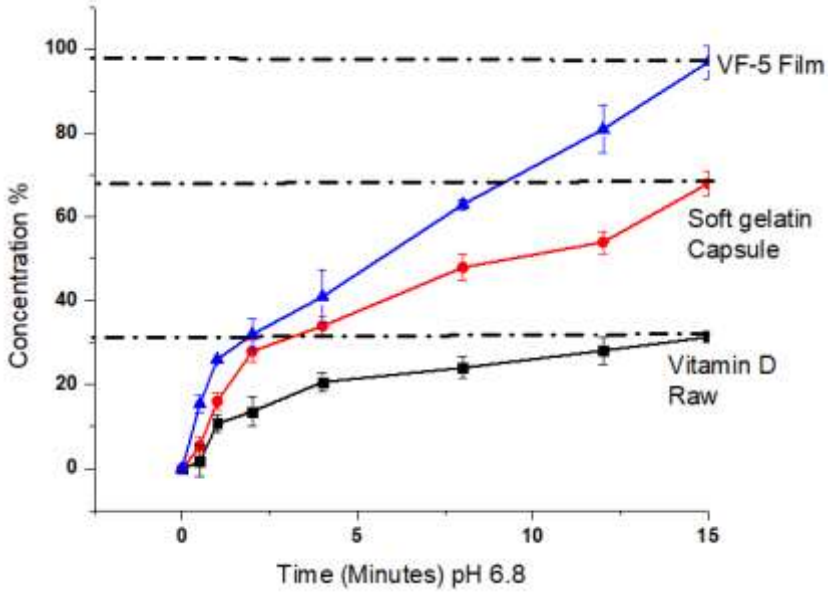

Fig. 3: Drug releases percentage from vitamin D soft gelatin capsule, Vitamin D suspension and from film (VF-5) at pH 6.8

Stability study

Manufactured film was tested for stability in accordance with ICH criteria by being kept at a temperature of 40°C and a relative humidity of 75°C for three months. The film samples were coated with aluminum foil and put in the stability chamber as described above. The samples were removed after three months and put through physicochemical testing, including assay, moisture content and folding endurance.

Ethical approval

All experimental protocols were approved by the Rashid Latif College of Pharmacy (RLCP) Ethical Review Board IRB No (RLCP/EP/112/2023) and they were carried out in accordance with the Declaration of Helsinki World Medical Association.

STATISTICAL ANALYSIS

The statistical analysis was performed using the Graph-Pad Prism v.5 program and included the one-way ANOVA and Tukey's test. The data (SD) were represented using the mean and standard deviation. The threshold for statistical significance was a *P* value of 0.05 (Mehmood *et al*., 2023).

RESULTS

Determination of drug entrapment efficiency

Take the vitamin D film already prepared, cut it with specific area (4cm^2), weight it and dissolve into buffer so that all AM mixed in buffer (ethanol and newly made pH 7.4 phosphate buffer USP, 30:70) and sonicate it.

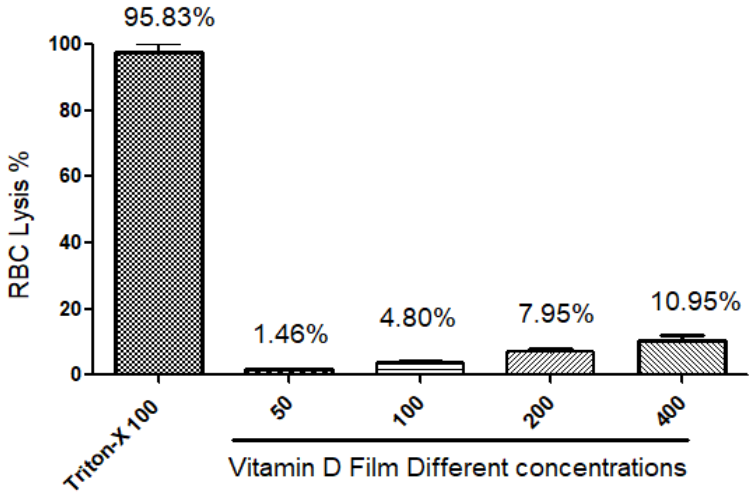

Fig. 4: Haemolysis graph of film with different concentrations

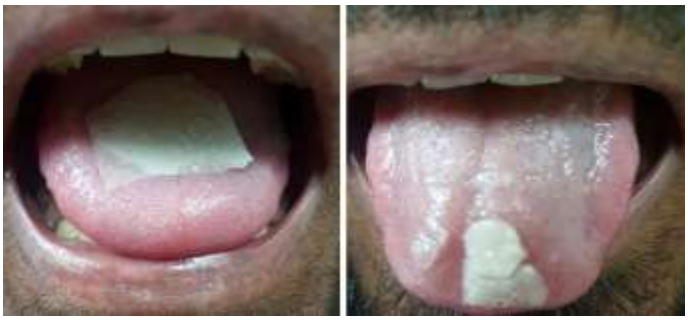

Fig. 5: Disintegration of film on tongue of person to observe its disintegrations within saliva

The prepared solution was diluted with mobile phase to determine the amount of vitamin D using an HPLC with a maximum wavelength of 265 nm (Barkat *et al*., 2017). The same technique was used to check each film VF-1 to VF-5. Results regarding drug entrapment were listed in a table 2. We found that the VF-5 formulation, in which we added the maximum amount of (MCC+CMC) had the highest drug entrapment. This formulation has been chosen for additional characterizations.

Physicochemical characterization

Various physicochemical parametric tests were used to evaluate the produced film. Weight variation, thickness, folding endurance and moisture content as shown in table 3. The effectiveness and repeatability of the formulation preparation procedure are gauged by the evaluation tests. It was determined that the films' thicknesses varied between 0.038±0.02 and 0.075±0.14 mm. According to reports, the weight fluctuation varied between 0.442±0.67 and 0.616 ±0.22 g. The folding endurance was discovered to rise from 440±11 to 450±12 as the chitosan concentration was raised from film batch VF-1 to VF-5. Additionally, moisture content and uptake rise from 10.20±1.42 to 11.80±1.27 and 12.10±1.71 to 13.70±1.25, respectively.

Scanning electron microscopy and Investigation of surface roughness by AFM

SEM analysis was used to determine the morphological characteristics of the film (VF-5). fig. 1 (B) shows a high pixel camera view of prepared film under day light. The SEM image of the film made from (MCC+CMC) (fig. 1A) clearly shows that the surface is uneven. It's possible that drying out caused the polymeric structure to shrink, resulting in the surface's unevenness and roughness throughout. The surface roughness of the film VF-5 was supported by AFM fig. 1 (C) as well. This roughness may increase due to increase (MCC+CMC) concentration. The structure of the film can be changed for a variety of purposes by adjusting the ratios of polymer and monomer, which can affect the physicochemical properties of the film cavities and in the interaction with guest molecules.

Fourier transform infrared spectroscopy

(MCC+CMC), HPMC E5, Vitamin D and film FTIR spectra are shown in fig. 3. All samples were evaluated using the 800-4000cm^{-1} scanning range. A band at 3213 cm^{-1} in the vitamin D3 spectrum was linked to O-H hydrogen bonds and bands at 2972 and 2881cm^{-1} were associated with C-H stretching. While a band at 890cm^{-1} may be attributed to the vibration of C= CH_2. Two more bands at 1550.23 and 1277.23cm^{-1} were associated with

the angular deformation of geminal dimethyl. The bands that were seen matched what was written in the literature (Colturato & Goveia, 2022; Glinka *et al*., 2021). The O-H stretching vibration peak on the HPMC was at 3498.52cm^{-1}, while the C-H stretching vibration peak was at 2945.57cm^{-1} (Javeer & Amin, 2014). The FTIR spectrum of pure (MCC+CMC) (fig. 3) exhibits a strong broad band at approximately 3390 cm^{-1} and a band at 1636 cm^{-1} corresponding to the stretching and bending modes of the surface hydroxyls; the peak at 2205cm^{-1} is associated with the asymmetrically stretching vibration of C-H in a pyranoid ring and the broad absorption peak at approximately 1059cm^{-1} is associated with the cellulose C-O. Film displayed peaks at 1271.22cm^{-1}, indicating the presence of vitamin D absorption band. This group's displacement ranged from 1550.23 to 1571.16cm^{-1}. Due to the overlap of small peaks, the in the film we cannot see polymers peaks. A single peak of MCC+CMC can be seen at a wavelength of 2236.19cm^{-1}.

Drug release study

The released profile of the vitamin D from the film was obtained by conducting dissolution at pH 6.8 for 15 minutes at varied intervals. A HPLC (Shimadzu, Germany) was used to detect the sample absorbance at a predetermined wavelength (265 nm maximum). At pH 6.8 film formulation VF-5 release more vitamin D, which may be due to the ionization of the R-COOH (carboxylic) group of (MCC+CMC).. The drug dissolution profiles of film VF-5 presented in fig. 3. The addition of sweetener and flavouring agent in the film did not significantly affect the release of vitamin D. Li, Jason Z., *et al* (Li *et al*., 1996) showed that the addition of (MCC+CMC) into oral disintegrating tablet increased the dissolution rate. Shimoda *et al* (Shimoda *et al*., 2009) showed that by incorporating more than 50% of (MCC+CMC) in dexamethasone containing ODF, 90% of the drug was released within 5 min. In the present study, an addition of 40% of (MCC+CMC) resulted in 40% of drug released in 5 min.

The hemolysis assay

The film hemolysis assay was performed as a rapid and accurate way to determine a material's compatibility with blood (Mehmood *et al*., 2020a; Mehmood *et al*., 2020b; Mehmood *et al*., 2023; Mehmood *et al*., 2022). When blood comes into contact with film, the hemolysis assay analyzes the erythrolysis and hemoglobin dissociation. Weights in mg (50, 100, 200 and 400mg) were immersed in blood for two hours after the film was cut. After that, blood compatibility was calculated using a spectrophotometer. PBS was used as the negative (not shown) and Triton-X, which had 95.83% lysis, was used as the positive. Different weights were used to assess blood compatibility and the findings for 50mg (1.64%), 100mg (4.80%), 200mg (7.95%) and 400mg (10.95%) were satisfactory. All lysis percentages were under 11% and it was under 6% for dosages of 50mg and 100mg. Our research indicates that hemolysis could not be considerably produced by hydrogel film. This might be because the polymer is biocompatible. Our findings imply that film has a long-lasting hemostatic potential for use due to its adaptable mechanical, physical and Bio properties and high capacity to cause blood coagulation.

In situ disintegration time

The mean in situ disintegration time was 56.13±3.12 second (40–60 second), which was in good agreement with the in situ disintegration time of 48.7±3.7 second, reported by Liew et (Liew *et al*., 2012). The in situ disintegration time results showed no statistically significant differences ($p>0.05$) among the formulations. In fig. 5, photographs of the film breakdown process on the tongue are displayed. Film formulations met the BP 2023 requirement for orodispersible formulation because they dissolved in less than a minute when exposed to water. According to BP, orodispersible formulations designed to be placed in the mouth where they quickly disperse before being swallowed.

Stability

Film formulation (VF-5) underwent stability testing in accordance with ICH guidelines with 40°C and 70% humidity for three months. Test factors for the stability study, including as thickness, weight fluctuation, folding endurance, moisture content and moisture uptake, were evaluated (results in table 4). No significant changes in the selected test parameters over the study period demonstrated the generated films' good physical stability.

DISCUSSION

Fast-dissolving drug delivery systems are rapidly gaining interest in the pharmaceutical industry. These systems either dissolve or disintegrate generally within a minute, without the need for water or chewing. Recently, fast-dissolving films are gaining interest as an alternative of fast-dissolving tablets. The films are designed to dissolve upon contact with a wet surface, such as the tongue, within a few seconds, meaning the consumer can take the product without the need for additional liquid. This convenience provides both a marketing advantage and increased patient compliance. These films may facilitate systemic medication delivery via intragastric and sublingual routes either by mouth (oral) or by mouth (oral and buccal) for local effect. Dosing is much easier with this type of technology medication, not just to those in need, such as children, the elderly, the bedridden and those with mental illness, but to the entire public as a whole population. We have used in this research two cheap polymers (MCC+CMC) and hydroxypropylmethyl cellulose to create an oral disintegrating film that contains cholecalciferol (Vitamin D3), a fat-soluble vitamin that aids in the body's absorption of calcium and phosphorus. In the previous research scientist used more expensive polymers to prepared oral films. But our used polymers

are very economical and easy available which can be best fit for commercial use. The goal of the current inquiry was to develop orally disintegrating films of vitamin D3 to improve patient comfort and compliance for pediatric or elderly patients due to its simplicity of administration. By using the solvent casting procedure which is best method we have prepared films were created. Due to limited funds we did not performed *in vivo* study after swelling it to observe it bioavailability. Furthermore we suggest to researchers to conduct clinical study on this.

CONCLUSION

We created a vitamin D-containing fast-dissolving oral thin film for the first time. The successful development of (MCC+CMC) and HPMC E5 containing film with vitamin D has potential for the treatment. Suggestive characteristics for a successful formulation include thickness, weight variation, folding endurance and moisture absorption. To analyze the surface shape and molecular interactions of the polymer used to make the film, its properties were examined using FTIR, SEM-AFM. These results imply that the current vitamin D-containing oral film may be helpful to administer the medication immediately in patients who limit their intake of other dosages.

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