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Utilization of Waste Eggshell Powder as an Excipient for Vitamin D3 Tablet Preparation

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ABSTRACT: Keeping in mind the health scenario in Kingdom of Saudi Arabia with respect to vitamin D3 (VD3) deficiency and its significant role in calcium homeostasis and human metabolism, this research is exploring the combination of eggshell (as a source of calcium) and VD3 as a very economical solution for this problem. Eggshells from local restaurant were collected, washed, ground, sieved, and characterized by Fourier transforms infrared spectroscopy (FTIR), scanning electron microscopy (SEM), differential scanning calorimetry (DSC), X-ray diffraction (XRD), and Brunauer−Emmett−Teller (BET) techniques. The results of FTIR, SEM, DSC, XRD, and BET indicate that eggshell powder (ESP) was properly processed. Directly compressed tablets containing 2.5 mg of VD3 (equivalent to 50,000 IU), that are based on the use of ESP as tablet filler, were manufactured based on mixing Avicel PH 101 with ESP in different ratios (9:1, 1:1, and 1:9) in addition to the use of both Avicel PH 101 and ESP alone as tablet filler. Tablets properties were evaluated according to USP30-NF25 pharmacopoeia tests in terms of weight variation test, drug content uniformity, tablet hardness, tablet friability, tablet disintegration, and in vitro dissolution profile. The VD3 contents were found to be 98.77−102.35% in all formulations. After 90 min of study, all formulations showed in vitro drug release content in the range of 99.29−101.05%. All of the tested parameters of ESP tablets were similar to those of commercial Avicel PH 101. All of the tested properties of tablets with ESP as a filler were found to be within the acceptable limits of the pharmacopeia recommendations. Therefore, ESP could be exploited for its use as a filler in direct compression tablets.

1. INTRODUCTION

Management of municipal solid waste (MSW) is a difficult task for every municipality department in any nation. MSW consists of organic waste (engendered due to the extensive use of food) and plastics (produced by the massive use of disposable stuff). Managing of discarded materials by orthodox approaches, such as incineration, land fill, and dumping results in several environmental issues which includes greenhouse gas emissions, groundwater contamination, and soil contamination. Keeping in mind the general contemporary circumstances and different varieties of solid waste produced, there lies an abundant possibility in creating such waste transformation techniques by which we can alter the waste material into other commercially valuable products, leading to economic and environmental sustainability.

Eggshells are easily collected waste materials from homes, dwellings, and hatcheries. One of the most prevalent wastes produced by the food processing industry is eggshell waste. Getting rid of eggshell trash damages the ecosystem. Cost, accessibility to disposal places, odor, flies, and abrasiveness are all problems with eggshell disposal. Despite its special qualities, it is frequently thrown away without being used again. However, they can be utilized to create items that can be sold, such as fertilizer, materials for artwork, food for humans and animals, and building materials, as well as to make collagen from the membranes.[1] Numerous review articles on eggshell waste demonstrate its broad potential for use in materials science.[2−4] It has already been discussed how eggshell waste can be used as a food supplement,[5] for organic synthesis,[6] catalysis,[7,8] and adsorption.[9,10] Patents exist for some eggshell-related technologies.[11,12] The inner and outer membranes of the shell as well as the calcified shell make up the eggshell. A little over 98.2% of the eggshell's material is calcium carbonate ($CaCO_3$), with a similar percentage (0.9%) each of magnesium and phosphorus (in the form of phosphate).[13] To supplement dietary sources, it is advised that individuals with osteoporosis take 400−500 mg of calcium daily. The primary purposes of calcium-containing medications, food supplements, and vitamin-mineral complexes are to treat osteopenia and

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osteoporosis concurrently and to avoid osteoporotic fractures.[14]

Pharmaceutical excipients are defined as substances other than the active pharmaceutical ingredient (API) that have undergone adequate safety evaluation and are purposefully used in a drug delivery system, according to the International Pharmaceutical Excipients Council.[15] The excipients' role was to transform the API into a format that was useful to the patient.[16] The direct compression method is the simplest technique to create a tablet using an API and excipients. The development of novel and coprocessed excipients as well as powerful tablet presses may be to blame for this trend given that more excipients may satisfy the standards for direct compression.[17,18] In pharmaceutical solid dosage forms, $CaCO_3$, a low-cost substance with a high surface area, excellent safety, biocompatibility, and biodegradability, is primarily utilized as a diluent.[19] Additionally, $CaCO_3$ has recently been shown to be an effective hydrophilic porous carrier for enhancing the oral bioavailability of medicines with low water solubility.[20−23]

Vitamin D3 (VD3) is a fat-soluble vitamin, which is practically insoluble in water and offered excellent solubility in organic solvents.[24,25] VD3 is necessary for maintaining bone health because it plays a crucial part in the human body's calcium homeostasis and metabolism.[26] Additionally, it is crucial for immune system regulation as well as control of body cell differentiation and proliferation. Therefore, it is thought that VD3 insufficiency raises the risk of a number of important nonskeletal chronic diseases, including autoimmune disorders, cardiovascular disease, and several cancers.[27] Calcium intake, either alone or in combination with VD3, has been linked to a decreased loss of bone mineral density (BMD). Reduced BMD loss is associated with a decreased risk of bone fractures. In postmenopausal women, calcium and VD3 may also slow the loss of BMD.[28] The combination of calcium and VD3 can alter the BMD or the frequency of osteoporotic bone fractures. Adults (over the age of 18) can effectively prevent and cure steroid-induced osteoporosis by taking calcium and VD3.[29−32] According to a recent analysis, emulsion methods or chemical precipitation of $CaCO_3$ micro/nanoparticles have been used to create the majority of the effectively constructed $CaCO_3$ carriers.[33] However, $CaCO_3$ micro/nanoparticle precipitation is tricky to replicate, and scaling up the process is frequently difficult, preventing practical application of these carriers. Preclinical research would also be necessary for thorough knowledge of the biosafety and in vivo degradation of the novel $CaCO_3$ particles. An intriguing solution to these problems is to use $CaCO_3$ from a natural source and change it to make it suitable for use as a drug delivery carrier.

ESP has been investigated for various studies as a low-cost material.[2−13] However, its application as a directly compressible filler in VD3 tablets has not yet investigated. Keeping in mind the above-discussed benefits of eggshells including being a source of natural and cost-effective source of calcium as well as its suitability to be used as an excipient/filler in tablets, the present research is an attempt to investigate the pharmaceutical application of the ESP as a direct compression excipient in tablet formulation and also the physicochemical properties of the physical mixture to provide a cost-effective prevention and treatment of the diseases related to the deficiency of calcium and VD3. Given the general contemporary circumstances and different varieties of solid waste produced, there lies an abundant possibility in creating such waste transformation techniques by which we alter the waste material into other commercially valuable products, leading to economic and environmental sustainability.

2. RESULTS AND DISCUSSION

2.1. Characterization of ESP. *2.1.1. Scanning Electron Microscopy (SEM).* Analyzing ESP using SEM provided detailed information about the external characteristics and structural features of the powder (Figure 1). ESP when

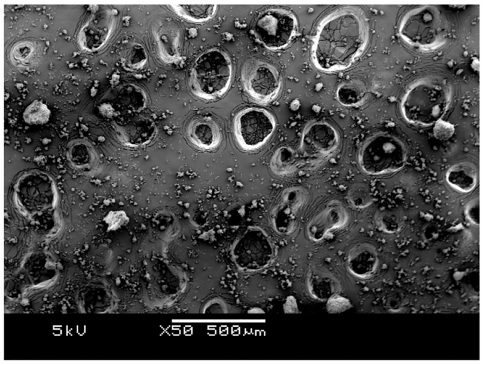

Figure 1. Scanning electron microscopy (SEM) image of eggshell powder (ESP) porous structure, revealing the presence of pores of varying size.

observed under SEM, irregularly shaped particles have uneven surfaces with various sizes, typically ranging from micrometers to tens of micrometers. As far as surface texture is concerned, granular or rough surfaces on the particles was observed. Eggshell is known to have a porous structure, and the SEM image reveals the presence of pores within the eggshell particles. These pores may vary in size and distribution and can be seen as voids on the surface of the particles. ESP has a high degree of porosity, which in turn imparts improved flow properties. Porous particles tend to flow more easily than nonporous particles because they can reduce interparticle friction. Improved flow properties can be advantageous in tablet manufacturing, as it ensures uniform distribution of the filler in the tablet blend, leading to more consistent tablet weights and content uniformity. The porosity of the ESP can also affect the tablet's compressibility. Highly porous particles may compress more readily under compaction, potentially resulting in tablets with a lower hardness.

2.1.2. Fourier Transform Infrared (FTIR) Spectroscopy. Eggshell is primarily composed of $CaCO_3$. In the FTIR spectrum, strong absorption bands at around 1420−1450 cm^{-1} and 870−880 cm^{-1} were observed. These bands correspond to the stretching vibrations of carbonate ions (CO_3^{2-}) in $CaCO_3$. The band at 710 cm^{-1} in an FTIR spectrum of ESP is usually associated with the out-of-plane bending (asymmetric) mode of the CO_3^{2-} ion. This occurs when the carbonate ions move out-of-phase with each other, resulting in a lower wavenumber band, which can be observed around 700−720 cm^{-1} (Figure 2).

2.1.3. X-ray Diffraction (XRD). When analyzing the XRD pattern of ESP, peaks corresponding to the crystalline phases present in the eggshell, primarily $CaCO_3$ (calcite) was observed at 2 theta value of 29.5°, 36.1°, and 47.7°. These angles correspond to the (104), (110), and (113) planes of calcite, respectively. The intensity and sharpness of these peaks depend on the crystallinity and purity of the ESP (Figure 3).

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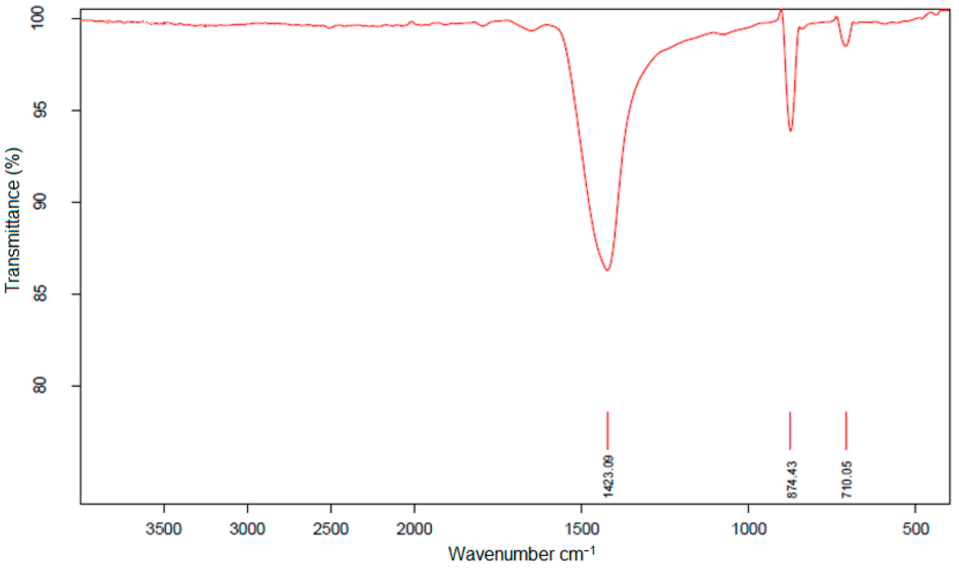

Figure 2. Fourier transform infrared (FTIR) spectra of ESP showing characteristic peaks of the material.

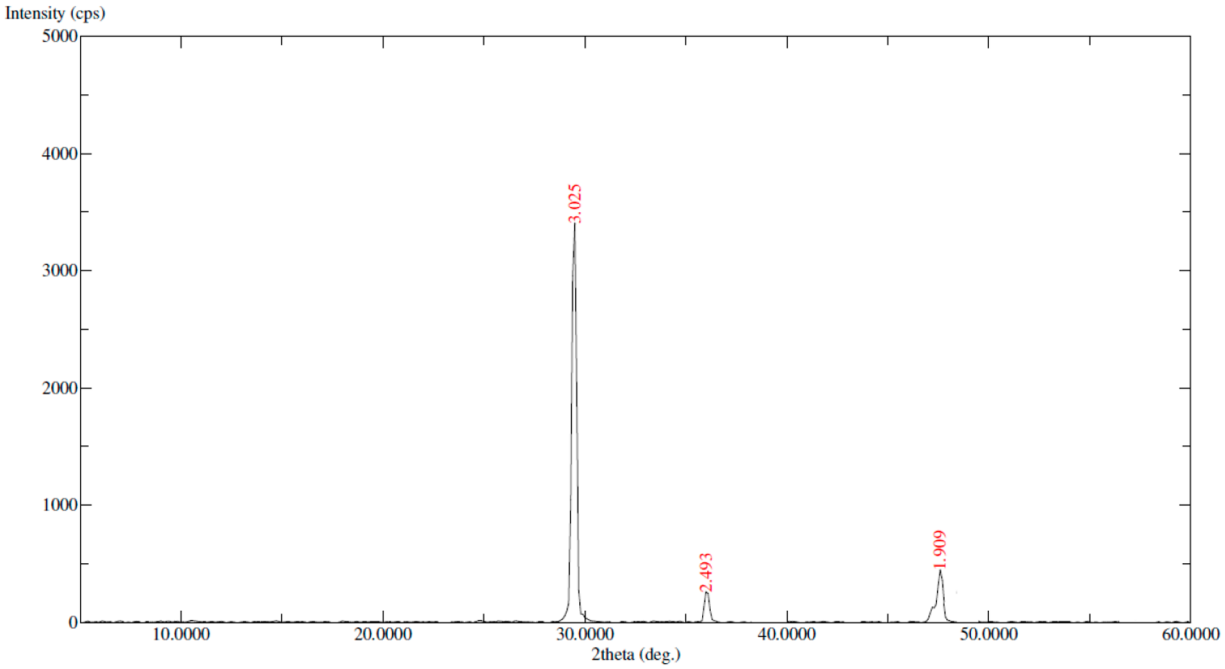

Figure 3. X-ray diffraction (XRD) spectra of ESP show peaks corresponding to the crystalline phases present in the eggshell.

2.1.4. Thermal Analysis. The differential scanning calorimetry (DSC) curve is given in Figure 4. The presence of endothermic peaks occurring between 50 to 100 °C was due to water evaporation. Its position in the curve depends on the moisture content of the sample. This peak represents the heat absorbed during the evaporation of any residual moisture present in the ESP. In addition to $CaCO_3$, ESP also contains traces of organic matter such as proteins or residual membranes. These organic components can also undergo thermal decomposition at specific temperatures, contributing to the observed peak at 220 and 290 °C. The most significant exothermic peak for ESP is related to the decomposition of $CaCO_3$, the primary component of eggshells. The heat release during this peak is associated with the breakdown of $CaCO_3$ into calcium oxide (CaO) and carbon dioxide (CO_2). The

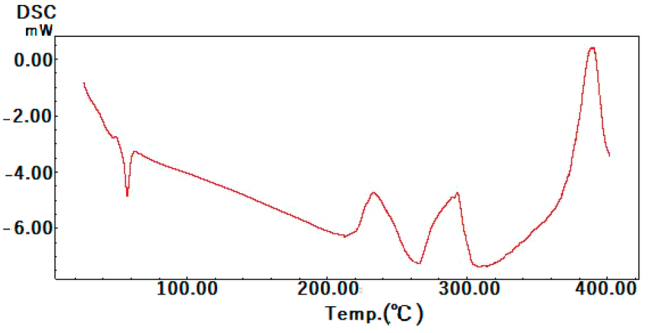

Figure 4. Differential scanning calorimetry (DSC) spectra of ESP showing peaks corresponding to the crystalline phases present in the eggshell.

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peak at 400 °C may correspond to the onset temperature at which this decomposition process occurs.

2.1.5. Brunauer–Emmett–Teller (BET) Analysis. BET analysis was used to calculate the surface area, pore volume, and micropore volume of the ESP sample. The ESP's BET surface area and t-plot external surface area were found to be, respectively, 3.1646 m^2/g and 4.6123 m^2/g. This value is in close agreement with the previously published report.[34] The sample's pore volume, which was found to be 0.019246 cm^3/g, indicates that the active site is close to the powder's outside surface. This should result in a better and more rapid interaction between the medication and the ESP. A larger pore volume (pore radius = 243.25 Å) in ESP can lead to improved flow properties. It can reduce interparticle friction, making the powder flow more freely and evenly during the manufacturing process. This can lead to better content uniformity in the tablets. Also, larger pores can prevent ESP from forming clumps or caking during storage and handling. This is important for maintaining the quality of the filler and ensuring consistent tablet production.

2.1.6. Powder Properties. The quality of the final preparation is influenced by the powder flow properties in a solid dosage form such as the angle of repose and compressibility. The characteristics of the powder, including density (both bulk and tapped), the angle of repose, Carr's index, and Haussner's ratio, were determined in this study for pure ESP, pure Avicel, ESP combined with Avicel, and commercially available chemically precipitated $CaCO_3$ both alone and in combination. The results were summarized in Tables 1 and 2. On comparing Tables 1 and 2, it can be inferred that ESP has similar properties when compared to the commercially prepared $CaCO_3$ and shows excellent flow properties either alone or in combination with Avicel. For powders having excellent flow properties, its angle of repose should be ideally between 25 and 30°. When angle of repose was studied for these powders and their mixtures, it was observed that either alone or in combination of Avicel, ESP performed similarly to the commercially available $CaCO_3$ and all combinations showed angle of repose in the range of 25.26–29.32°. Also, effect of particle size of ESP on micromeritic performance was analyzed by reducing its particle size by ball milling. Reduction in size by ball milling did not improve the micromeritic properties of the ESP and hence ball milling was found to be detrimental. Therefore, on the basis of micromeritics data, it could be concluded that ESP possesses required flow property which a potential candidate is expected to possess to be considered as a filler in tablet making process.

Table 1. Micromeritics of Pure Eggshell Powder (ESP) and in Combination with Avicel

ESP: Avicel ratio	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner ratio	Angle of repose (deg)
10:0	1.15	1.50	23.46	1.31	28.35
9:1	0.95	1.64	22.20	1.73	25.74
1:1	0.60	0.75	20.00	1.25	25.26
1:9	0.26	0.31	14.79	1.17	28.07
0:10	0.21	0.27	13.65	1.09	27.40

Table 2. Micromeritics of Commercial Calcium Carbonate ($CaCO_3$) and in Combination with Avicel

$CaCO_3$: Avicel ratio	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner ratio	Angle of repose (deg)
10:0	1.11	1.46	24.07	1.31	29.32
9:1	1.05	1.37	22.73	1.28	26.12
1:1	0.61	0.77	20.42	1.25	25.71
1:9	0.25	0.30	19.89	1.23	28.61
0:10	0.22	0.26	20.56	1.19	27.81

2.2. Tablet Evaluation. Table 3 shows the properties of directly compressed tablets containing 2.5 mg of VD3 (equivalent to 50,000 IU). These tablets were manufactured by varying the composition of the filler based on the ratio between Avicel PH 101 and EPS.

2.2.1. Weight Variation Test and Drug Content Uniformity. Weight variation tests are performed during tablet manufacturing to ensure the consistency and uniformity of the tablets being produced. The directly compressed tablets containing VD3 showed weight uniformity, in which all tablet formulations' weights were in the range of 0.196–0.198 g with low standard deviation values. The VD3 content in all of the examined tablet formulations exceeded 95%, aligning with the United States Pharmacopoeia (USP) guidelines, irrespective of the varying compression forces applied. The calculated acceptance value (AV) for all tablet formulations is very small, indicating uniform VD3 content in the formulations. Furthermore, it was noted that neither the type nor the proportion of the polymers used in the matrix formation nor the compression force had any effect on the VD3 content.

2.2.2. Tablet Hardness. All directly compressed tablet formulations showed hardness in the range 2.63–15.31 kp, which is acceptable for the immediate release tablet formulations. Moreover, blending Avicel PH 101 and EPS resulted in enhancing tablet hardness to more than 4.9 kp. However, the use of ESP alone as a tablet filler resulted in reducing tablet hardness to 2.63 ± 0.22 kp, but the tablet hardness value is still in the acceptable range. It will ensure that the tablet can withstand the stresses it may encounter during handling, packaging, and transportation without breaking or crumbling.

2.2.3. Tablet Friability. All VD3-loaded tablets prepared by direct compression showed acceptable friability values (less than 1%), which were according to the USP friability compendial guidelines (USP29–NF24) in the corresponding monograph > TABLET > FRIABILITY. In addition, the highest friability percentage was recorded for the tablets manufactured based on ESP alone as a tablet filler (0.84%), but even this value lies in the acceptable friability range. These data could explain the lower hardness value of the tablets containing ESP alone as filler in comparison to the tablets prepared by blending Avicel PH 101 and EPS or tablets based on Avicel PH 101 only as a filler.

2.2.4. Tablet Disintegration. Most of the manufacture tablets showed disintegration time less than 90 s, except tablet manufactured by blending Avicel 9:1 ESP that showed disintegration time of 154 s. The factors such as hardness and compression force might be responsible for the increased disintegration time of the Avicel 9:1 ESP blend. The hardness and compression force could also be responsible for the variation in the disintegration time of different formulations. Although, the disintegration time of the Avicel 9:1 ESP blend was enhanced, but it was within the acceptable limit. The enhanced disintegration rate of the manufactured tablets

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Table 3. Evaluation of Directly Compressed Tablets Containing Vitamin D3 (VD3) Manufactured by Blending Avicel and ESP in Different Ratios

Tablet formulation	Weight (g)	Content uniformity (mg)	VD_3 content (%)	Friability (%)	Hardness (kp)	Disintegration time (s)	VD_3 IDR (%)	VD_3 DE (%)
Avicel alone	0.196 ± 0.003	3.02	100.97 ± 1.208	0.25 ± 0.02	10.78 ± 0.57	77.8 ± 2.8	34.27 ± 0.71	76.51 ± 0.53
Avicel 9:1 ESP	0.196 ± 0.002	3.46	102.35 ± 1.045	0.67 ± 0.06	4.92 ± 0.50	154.0 ± 13.2	35.26 ± 0.44	76.85 ± 0.25
Avicel 1:1 ESP	0.196 ± 0.001	3.31	98.77 ± 1.329	0.11 ± 0.01	15.31 ± 1.27	89.4 ± 4.2	37.39 ± 1.01	78.53 ± 0.29
Avicel 1:9 ESP	0.197 ± 0.002	1.99	99.91 ± 0.797	0.22 ± 0.02	11.96 ± 1.50	16.5 ± 1.8	39.21 ± 0.54	79.56 ± 0.10
ESP alone	0.198 ± 0.002	2.29	101.49 ± 0.915	0.84 ± 0.04	2.63 ± 0.22	78.2 ± 3.2	40.4 ± 0.64	81.84 ± 0.32

containing VD3 is expected to synergistically affect the drug dissolution behavior.[35,36]

2.2.5. In Vitro Dissolution. The in vitro dissolution profile of VD3 from different directly compressible tablets at various time intervals is displayed in Figure 5. All tablet formulations

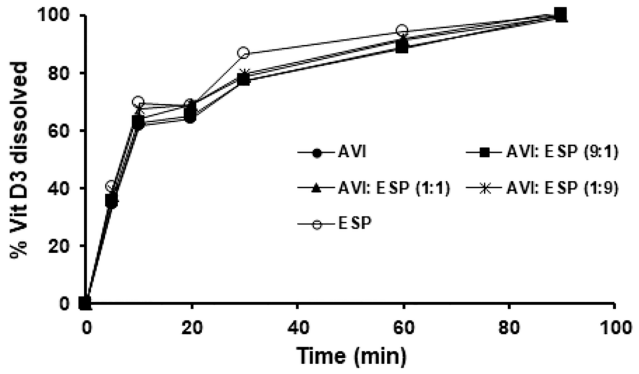

Figure 5. In vitro dissolution profiles of vitamin D_3 (VD3) from directly compressed tablet formulations at pH 6.8 and 37 °C.

showed immediate drug release profile and released more than 99% after 90 min of study. The cumulative % release of VD3 from formulations AV1, ESP, AV1:ESP (1:1), AV1:ESP (1:9), and AV1:ESP (9:1) after 90 min of study was 99.29 ± 1.01, 100.27 ± 0.31, 99.37 ± 0.93, 101.05 ± 0.49, and 99.95 ± 0.20%, respectively. As a consequence, ESP showed a similar dissolution profile for VD3 as recorded for Avicel. The drug release profile of VD3 was not significantly changed when ESP was studied in combination with commercial Avicel in different proportions, such as 1:1, 1:9, and 9:1. These findings suggested that ESP had similar micromeritics properties as those of commercial Avicel and hence can be utilized as an alternative of commercial Avicel as a low cost directly compressible material. In addition, it can be utilized in combination with commercially available directly compressible materials in various proportions. The results of initial dissolution rate (IDR) and dissolution efficiency (DE) for different tablet formulations are displayed in Figure 6. The % IDR of VD3 from formulations AV1, ESP, AV1:ESP (1:1), AV1:ESP (1:9), and AV1:ESP (9:1) was 34.27 ± 0.71, 40.40 ± 0.64, 37.39 ± 1.01, 39.21 ± 0.54, and 35.26 ± 0.44%, respectively. However, the % DE of VD3 from formulations AV1, ESP, AV1:ESP (1:1), AV1:ESP (1:9), and AV1:ESP (9:1) was 76.51 ± 0.53, 81.84 ± 0.32, 78.53 ± 0.29, 79.56 ± 0.10, and 76.85 ± 0.25%, respectively. The IDR and DE of VD3 from different tablet formulations were not significantly different, but ESP alone showed the maximum IDR and DE of VD3 compared to other formulations investigated. Therefore, ESP can be used as a

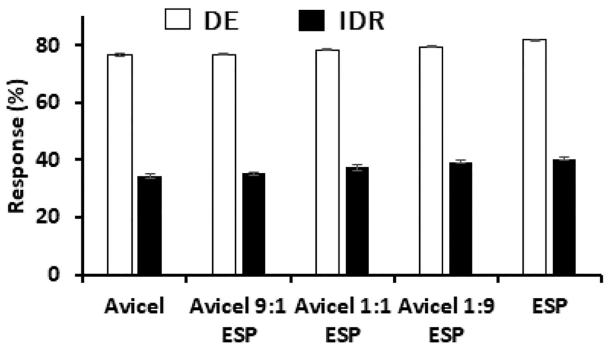

Figure 6. In vitro initial dissolution rate (IDR) and dissolution efficiency (DE) of VD3 from directly compressed tablet formulations at pH 6.8 and 37 °C.

low-cost material either alone or in combination with commercially available, directly compressible materials. The major limitation of this study is that the in vivo pharmacodynamics and pharmacokinetics potential of obtained ESP tablets were not explored.

3. CONCLUSIONS

For the purpose of exploring as well as comparing the suitability of the tablets containing eggshell as an excipient (as well as a source of calcium) along with VD3, ESP was prepared and characterized for its physicochemical characteristics (FTIR, DSC, SEM, XRD, and BET) and micromeritic properties. On the basis of characterization results, it can be concluded that ESP possesses required features to be used as a filler in tablet preparation. Pharmaceutical powders' micromeritic characteristics are one of the key factors carefully considered before being formulated into different solid drug delivery systems. This research revealed from tapping experiments, which simulate the production process, that ESP products possessed similar micromeritic properties with respect to the synthesized $CaCO_3$. Tablets of VD3 prepared with ESP as a filler exhibited excellent properties in terms of weight variation, drug content uniformity, hardness, friability, and disintegration as well as in vitro dissolution profile. On the basis of the results obtained in this research, it can be concluded that ESP could be exploited for making tablets in order to reduce the cost of treatment of hypovitaminosis D as well as calcium supplementation by replacing the synthesized $CaCO_3$ with the highly absorbable natural $CaCO_3$ obtained from the waste eggshell. This waste management approach will also contribute to the circular economy of the country. ESP can be used as an excipient for other drug delivery systems in future studies. Furthermore, pharmacokinetics and pharmaco-

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dynamics studies are required to explore the complete potential of prepared VD3 tablets for commercial exploitation in future studies.

4. MATERIALS AND METHODS

4.1. Materials. VD3 (cholecalciferol) was received as a kind gift sample from Riyadh Pharmaceuticals (Riyadh, Saudi Arabia). Commercially available microcrystalline cellulose (Avicel PH101) was provided by Serva Feinbiochemica (Heidelberg, Germany). Magnesium stearate was procured from Riedelde Han (Seelze, Germany). Potassium dihydrogen orthophosphate and sodium hydroxide were provided by E-Merck (Darmstadt, Germany). Eggshells was collected from restaurants (Riyadh, Saudi Arabia) that serve boiled eggs in the locality. The other materials and reagents used were analytical grade.

Keeping in mind the background of the waste management and the salient features possessed by the ESP, it is desired to put to use this powder in tablet making and exploit its features as an excipient. This work was carried out in phased manner which includes:

4.2. Collection of the Waste Eggshell. Eggshells was collected from restaurants that serve boiled eggs in the locality. The shells of boiled eggs are chosen because, after boiling, everything inside the egg solidifies, making it very easy to remove.

4.3. Processing of Eggshell. The collected eggshell was boiled in deionized water for 30 min to kill pathogens. These shells were dried in a hot air oven at 80 °C for 2 h. The dried eggshell was crushed and pulverized by using a porcelain mortar and pestle. This study used ESP that passed a 200 mesh sieve. A medium-sized eggshell in its entirety contains between 750 and 800 mg of elemental calcium.[2,4]

4.4. Characterization of the Obtained ESP. For the assessment of the properties of ESP, it was characterized by the following techniques to assess its nature:[2]

4.4.1. SEM. SEM is used to examine the surface morphology and microstructure of materials at a high resolution. Micrographs of the samples were obtained with a Hitachi S-510 SEM (voltage 25 kV, secondary electron images) (Hitachi Scientific Instruments Ltd., Tokyo, Japan) in order to comprehend the surface of the ESP.[9]

4.4.2. FTIR Spectroscopies. In order to examine the various kinds of functional groups found in the ESP, FTIR spectra with a resolution of 0.5 cm^{-1} were obtained in the 4000−600 cm^{-1} region. These spectra were recorded to know about the chemical structure, phase and polymorphy, crystallinity, and molecular interactions.[9]

4.4.3. XRD. Diffraction methods such as XRD can be used to pinpoint differences in the crystallinity of eggshell $CaCO_3$. A diffractometer was used to get the ESP's XRD spectra. For the purpose of recording XRD spectra, 40 kV and 25 mA of voltage and current were used, respectively. The spectra were collected at a diffraction angle between 3 and 60° and a step width of 0.05 °C.[10]

4.4.4. Thermal Analysis. A DSC was used to evaluate the ESP's thermal properties. Each sample was precisely weighed and placed in sealed aluminum pans. A control pan was also used as a reference. For this investigation, a temperature range of 25−400 °C with a heating rate of 10 °C/min was used. 50 mL/min of nitrogen gas was purged from the system.[10]

4.4.5. BET Surface Area and Pore-Size Distribution. The five-point BET method was utilized to calculate the BET surface area of ESP using AutoPore IV 9,500, Micromeritics Instrument, USA. BET was measured in duplicate with nitrogen at a constant temperature (77.4 K) after degassing 0.35g of the sample for 12 to 15 h at room temperature. Pore size distribution of eggshell $CaCO_3$ was determined with the same instrument. Mercury intrusion at low pressures ranged from 3.59 to 206.64 kPa. The pressure during the high-pressure mercury intrusion varied from 206.64 kPa to 206.78 MPa. Equilibration took 10 s for both high-pressure intrusion and low-pressure intrusion.[9,10]

4.4.6. Micromeritics of ESP. The production of solid dosage formulation, which is mostly utilized for physical, mechanical, and chemical processes, must take micromeritics into account.[37] The micromeritics properties of directly compressible materials are also important for their quality control tests. Therefore, micromeritics studies of ESP were determined in this work. By adding a measured amount of powder to a calibrated cylinder, measuring the volume (bulk volume), tapping the cylinder the appropriate number of times, and then measuring the volume again (tapped volume), the bulk and tapped densities may be calculated.[38] Equations listed below can be used to compute the density for bulk and tapped. The resulting values will then be used to derive a number of other important properties of a powder, such as the Hausner's ratio and the Carr's Index (compressibility index), which will be calculated from the following equations:[39]

$$\text{Bulk density } (\rho_b) = \frac{\text{Mass taken}}{\text{Bulk volume } (V_b)} \quad (1)$$

$$\text{Tapped density } (\rho_t) = \frac{\text{Mass taken}}{\text{Tapped volume } (V_t)} \quad (2)$$

$$\text{Compressibility Index} = \frac{\rho_t - \rho_b}{\rho_t} \times 100 \quad (3)$$

$$\text{Hausner ratio} = \frac{\rho_t}{\rho_b} \quad (4)$$

4.4.7. Angle of Repose. The method, which involves allowing powder to flow through under the influence of gravity without any additional work and allow it to gather into a conical heap on a planar surface, is said to be the most traditional method for characterizing the flow qualities of powder.[39,40] The flow of powder is poorer the higher the angle of repose.

4.5. Tablet Compression. Directly compressed tablets containing 2.5 mg of VD3, which are based on the use of ESP as tablet filler, were manufactured based on mixing Avicel PH 101 with EPS in different ratios (9:1, 1:1, and 1:9) in addition to the use of both Avicel PH 101 and ESP alone as tablet filler. In addition, magnesium stearate was used as a tablet binder in a concentration of 1%. Using a tumble mixer (Turbula T2C, Switzerland), the formula weight of Avicel PH 101 with EPS and VD3 was blended for 10 min. The powder mixture was then mixed for a further 2 min after the addition of magnesium stearate. Using a Korsh single punch machine with 9 mm shallow concave punches (Erweka, EKO, Germany), the powder was compressed into 200 mg tablets. In anticipation of further characterization, the compressed tablets were kept in sealed glass bottles in a chamber at 24 ± 2 °C and at 40 ± 5% relative humidity (measured values).[40]

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4.6. Tablet Evaluation. Tablets properties will be evaluated according to USP30-NF25 pharmacopoeia tests in terms of the following parameters:

4.6.1. Weight Variation Test. A digital balance (Shimadzu, EB-3200D, Tokyo, Japan) was used to weigh each of the 20 tablets individually. The average weight with standard deviation was then derived from the individual weights.[40]

4.6.2. Drug Content Uniformity. The AV of VD3 was assessed in accordance with the general harmonized chapter "USD 34−905-UNIFORMITY OF DOSAGE UNITS". Each of the ten units was placed in a volumetric flask with a capacity of 100 mL, to which 70 mL of methanol was added. The dispersion was then sonicated to dissolve the dosage forms, and the volume was then brought up to 100 mL with buffer. A reported HPLC method at 254 nm was used to calculate the quantity of VD3.[25] Calculations were made for the average content and the relative standard deviation.

4.6.3. Calculation of AV for Content Uniformity. The following formula was used to determine the AV for weight variation and consistency of dosage unit "content":[39]

$$AV = |M - \bar{X}| + ks \quad (5)$$

Where $\bar{X}$ is the average of the weights or contents, k is a constant that depends on the sample size: for 10 tablets, it is 2.4; for 30, it is 2.0. Depending on the sample mean ($\bar{X}$), M is a constant:

$$M = \bar{X} \text{ if } 98.5 \leq \bar{X} \geq 101.5$$

$$M = 98.5 \text{ if } \bar{X} < 98.5$$

$$M = 101.5 \text{ if } \bar{X} > 101.5$$

The estimated AV should be less than 15.0 (L1), and no one unit should differ from the reference value M by more than L2% (typically, 25%). No unit must be less than 0.75 M and no unit must be greater than 1.25 M for L2.

4.6.4. Tablet Hardness. Pharmatest Test System (WHT 32.V02.09.00/15, Multicheck, Germany) assessed the tablet hardness (tablet crushing strength). The crushing force that causes a tablet to break when it is placed between two anvils was recorded, and the average hardness and standard deviation values were calculated.[40]

4.6.5. Tablet Friability. VD3-loaded tablets were evaluated for friability by friabilator ((Type TA3R, Erweka Apparatebau, Heusenstamm, Germany) according to USP 1216 "Friability Test".[40] Twenty tablets were weighed (W_1) before being given to the friabilator drum, which was turned 100 times in four min, dedusting the tested tablet first. After the fines were removed from the tablets, they were reweighed (W_2), and the loss percentage was determined by $100 \times (W_1 - W_2)/W_1$.

4.6.6. Tablet Disintegration. According to the USP30-NF25 specifications for tablets intended for immediate release, an in vitro disintegration test was evaluated. To determine how long it takes for tablets to disintegrate, six tablets were placed in the basket rack assembly of the disintegration tester (Electrolab, ED-21, Mumbai, India). To prevent tablets from floating in distilled water kept at 37 ± 2 °C, six discs were utilized.[40]

4.6.7. In Vitro Dissolution. ESP tablets were given an in vitro drug release test utilizing a USP Dissolution Apparatus II; Paddle type (Caleva Ltd., Model 85T). 500 mL aliquot of distilled water with a pH of 6.8 was used for the dissolution experiment at a temperature of 37 ± 0.5 °C. The paddle's rotational speed was set at 50 rpm. At 5, 10, 20, 30, 60, and 90 min, 5 mL samples were taken, and the solution's response was determined using HPLC method at a wavelength of 254 nm. A documented HPLC technique at 254 nm was used to calculate the amount of drug release.[25] The % dissolution of VD3 at initial time point (5 min) was taken as IDR. However, the % dissolution of VD3 after 30 min time-point was taken as DE.

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Notes

The authors declare no competing financial interest.

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