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THE EFFECT OF TABLET MAKING ON THE MIGRATION OF CYANOCOBALAMIN FROM GRANULES DURING DRYING

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ABSTRACT

The migration of cyanocobalamin upon drying of its wet granules was studied through the formulation of different granules using different diluents (lactose monohydrate and anhydrous dibasic calcium phosphate), different binders in different concentrations; polyvinyl pyrrolidone (PVP k_{25}), hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), and gelatin at different drying temperatures (50°C and 70°C). Also, different layers of the dried granulation bed were separately compressed into their respective tablets and evaluated. The *in vitro* drug release from different formulated tablets was performed.
The results showed that, granules prepared with dibasic calcium phosphate showed relatively a higher migration for the drug than those prepared with lactose. Also, drug migration decreased with increasing the binder concentration and viscosity.

Mottling was extensively observed for batches prepared with low viscous binder solutions, while, it is diminished on using a highly viscous binder solutions. The tablets prepared with 10 % w/w gelatin were found to be the least mottled ones. In addition, they showed least friability percentage, highest hardness value, highest disintegration time and lowest dissolution rate. However, those prepared with 0.5 % MC showed highest friability percentage, lowest hardness value, lowest disintegration time and high dissolution rate. Generally, increasing the binder concentration resulted in slowing both mottling and the *in vitro* drug release from tablets.

INTRODUCTION

Compressed tablets are one of the most widely used dosage forms for the administration of orally effective therapeutic agents. They must be uniform in weight and in drug content of the individual tablet. Also, they must be elegant in appearance and must have the characteristic shape, color, necessary to identify the product.

Owing to their wide-ranging of physicochemical and mechanical properties, pharmaceutical powders and their blends frequently exhibit poor flow and compaction behavior [1].

Thus, an intermediate step, granulation is usually required in solid dose manufacture to produce a free-flowing material with good compression characteristics. Wet granulation has been, and continues to be, the most widely used agglomeration process [2]. But migration of soluble, low-dosage, highly potent drugs or of colored additives upon drying of their wet granules may represent a serious problem. This problem is the movement of the solutes from granule to granule, upon drying, which may result in gross maldistribution of the active drugs or the colored additives. As a result, an excessive dose variation may occur within the same batch of tablets. Also, the migration of the color may give rise to a tablet with a mottled appearance.

The objective of this work was to prepare cyanocobalamin granules, using different diluents, binders in different concentrations, and using different drying temperatures. The effect of these variables on the extent of cyanocobalamin migration upon drying of its wet granules was examined. In addition, the dried granules were prepared in tablet form, in order to study the effect of drug migration on the physical properties of these tablets.

EXPERIMENTAL

Materials

Lactose monohydrate (Foremost Food Co., San Francisco , CA 94104). Cyanocobalamin, calcium phosphate anhydrous, gelatin USP, and talc (Sigma Chemical Co., St. Louis, MO 63178). Polyvinyl pyrrolidone (PVP k25), 40000 (G.A.F. Corp., New York, USA). Methyl cellulose, (3000 - 6000) and hydroxypropyl methylcellulose, 40000 (Dow Chemical Co., USA). Disodium hydrogen phosphate (Prolabo, Chemicals, Paris, France).

Equipment

U.V. spectrophotometer (Jasco, V-530, Japan). USP standard sieves. Hot air ovens (Heraeus GS model B 5042, Gering model SPA-Gelman, Instrument No. 16414, Germany). Rotary viscometer (Haake Inc., Germany). MSE Minor Centrifuge (MSE scientific instruments, Manor Royal, Crawley RH/0200 sussex, England). Single punch tablet machine (Model EKO), tablet hardness tester (Model TB 24), Roche friabilator (Model TA 3R), tablet dissolution test apparatus (Model DT), and USP disintegration apparatus (Model ZT 3), (Erweka-Apparatebau, GmbH, Germany). Micrometer (Mitutoyo Corporation, Japan).

Methodology

I. Preparation of different binder solutions and determination of their viscosity

Four different types of aqueous binder solutions in different concentrations were prepared. These binders were; PVP k_{25} (5, 10, and 15% w/w), MC (0.5, 1, and 1.5% w/w), HPMC (0.5, 1, and 1.5% w/w) and gelatin (2.5, 5, and 10% w/w). The viscosity values of different types of binder solutions were determined using rotary viscometer which was thermostatically controlled at 30°C ± 0.5°C (Table (2).

II. Preparation of Cyanocobalamin wet granules.

Migration of cyanocobalamin was studied through the preparation of its granules using different diluents, binders and drying temperatures. Two formulations were prepared; formula A and formula B. Their constituents are illustrated in the following table:

Formula	Ingredients	Quantity per 200 mg of granules (weight of one tablet)
(A)	Cyanocobalamin	125 µg
	Lactose monohydrate	199.875 mg
	Binder solution	q.s.
(B)	Cyanocobalamin	125 µg
	Anhydrous calcium phosphate	199.875 mg
	Binder solution	q.s.

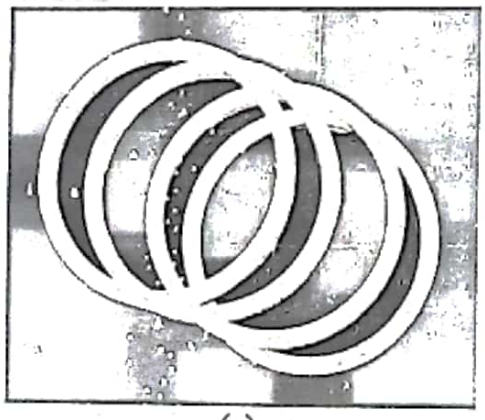
The granules were prepared by wet massing of lactose monohydrate, in case of formula A, or anhydrous calcium phosphate, in case of formula B, with the binder solution (PVP, MC, HPMC, or gelatin) in which the specified amount of the drug has been previously dissolved. The wet mass was kneaded for 10 min. until homogenous colored material was obtained. Wet screening was accomplished by passing the wet granulated mass through a 2 mm sieve (mesh number 10). A control experiment was performed for both lactose and calcium phosphate by applying the same procedure, using water as granulating fluid.

III. Drying of Cyanocobalamin wet granules.

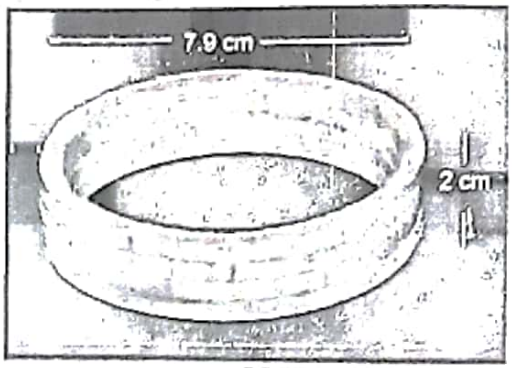
For each batch, the wet granules were then divided into two equal portions and placed in two similar drying cells. One cell was dried at 50 ± 1°C and the other was dried at 70 ± 1°C in two different drying ovens for 24 hours.

Drying cell

The drying process was carried out in a special drying cell consisting of four layers to facilitate the determination of cyanocobalamin concentrations at various depths in a granulation bed. The thickness of each layer was 0.5 cm with a total height of 2 cm. The cell was open from both ends of the cylinder formed by the layers; the opening was 7.9 cm in diameter (Figure 1).



(a)



(b)

Fig. (1): The drying cell employed for drying of wet granules.
(a) Assembled drying cell.
(b) Partially disassembled drying cell.

When it was used for migration studies, the drying cell was placed on a drying oven tray lined with a paper. The granules in the bottom layer were exposed to the paper during the drying process. The wetted granules, after being wet sieved, were filled into the drying cell with a spatula.

IV. Determination of cyanocobalamin concentration in different layers.

A) Sampling procedure

After drying, the top layer of the drying cell was carefully removed. Then, the top layer of the dried bed was removed by a flat blade, mixed thoroughly, and sampled for determination of drug concentration. Three samples, weighing 200 mg each, were accurately weighed from the top layer of the dried bed and used for subsequent determination of drug concentration. The procedure was repeated for the core layers (second, and third layers), and also for the bottom layer.

B) Cyanocobalamin assay method

i) For lactose granules (formula A)

Each sample was dissolved in 3 ml of distilled water. The absorbances of the dissolved drug in samples were measured at 360 nm using distilled water as a blank. The quantity of cyanocobalamin, in each layer, was determined and the percentage of drug in each layer was calculated.

ii) For calcium phosphate granules (formula B)

Each sample was dissolved in 5 ml of distilled water. The dissolved samples were then centrifuged for 15 min. and the absorbance of the drug in supernatant was measured at 360 nm using distilled water as a blank. The quantity of cyanocobalamin, in each layer, was determined and the percentage of the drug in each layer was calculated. Also, the results of drug percentages in the different layers for the control experiments were calculated.

C) Data treatment

To specify the extent to which the drug migrated in a numerical value, the concept of a coefficient of migration was employed. This concept was developed by Warren and Price, [3]. There are four layers in the drying cell, and each layer will be compared with the others. On this basis, a comparative difference (D) of the average

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assay values of layer 1 with layer 2, layer 1 with layer 3, layer 1 with layer 4, layer 2 with layer 3, layer 2 with layer 4, and layer 3 with layer 4 was calculated. In general, the equation for calculating the comparative difference between two layers (j and j') is:

$$D_{j\text{-}j'} = \frac{\left|L_j - L_{j'}\right|}{\frac{2\sum^{N}_{j=1} L_j}{N}} \qquad \text{(Equation 1)}$$

Where;

L_j represents the average of three assay values in a given layer.

$L_{j'}$ is the average assay value in another layer.

$\Sigma^{N}_{j=1} L_j$ is the sum of the average assay values for N layers.

N is the number of layers in the drying cell.

It is postulated that, the drug percent of the most divergent system using an open drying cell after drying can be represented as 200 %, 0 %, 0 %, and 200 % for layers: 1 (upper layer), 2 (second layer), 3 (third layer), and 4 (base layer), respectively, where the drug has migrated from the two intermediate inner layers (second and third layers) to the two exposed evaporating surfaces (upper and base layers). Using equation (1), the classification differences would be: $D_{1\text{-}2}$ = (200-0)/200 =1, $D_{1\text{-}3}$ = (200-0)/200 =1, $D_{1\text{-}4}$ = (200-200)/200 =0, $D_{2\text{-}3}$ = (0-0)/200 =0, $D_{2\text{-}4}$ = (0-200)/200 =1, $D_{3\text{-}4}$ = (0-200)/200 =1, and total = 4. So, the coefficient of migration is 4/4 = 1.

On the other hand, the most uniform system in a migration study using an open drying cell after drying can be represented as layer 1 = layer 2 = layer 3 = layer 4 = 100 %. From equation (1), the classification differences would be zero in all cases and the coefficient of migration would be 0/4 = 0.

It follows that, as the coefficient approaches one, the extent of migration is greater, but, if the coefficient approaches zero, the extent of migration is less. Results showing the different values of migration coefficient using different diluents, binder solutions and drying temperatures are shown in Table (3).

D) Statistical analysis of data

Spearman's rank correlation method was used to determine a correlation, if any, exists between the extent of cyanocobalamin migration and increasing the viscosity of binder solution.

Preparation of Tablets

Lactose granules, (formula A), dried at 50°C were used for tabletting. Where, the upper layer of the granulation bed (representing the highest drug concentration), and the third layer of the granulation bed (representing the lowest drug concentration), were separately compressed into tablets. For each binder, the lowest and the highest binder concentration containing formulations were chosen for subsequent compression into tablets. These prepared formulations are as shown in Table (1).

Each layer of granules was passed through mesh screen 1.6 mm. The reduced size granules were then mixed, in a rotating bottle, with 1% magnesium stearate and 2% talc for 10 min. The mixed components of each formula were then compressed into tablets using a single-punch tablet machine (9 mm diameter). The tablet weight was adjusted to 200 mg. The tablets were then visually inspected for mottling and evaluated for; weight variation, drug content, thickness, friability percentage, hardness, disintegration time, and *in vitro* drug release.

***In vitro* Release Study**

Drug release from different tablet formulations was performed using tablet dissolution apparatus at 50 rpm. The dissolution medium was composed of 50 ml phosphate buffer of pH 7.4, thermostatically maintained at 37±0.5°C and contained in a beaker of 150 ml capacity. Samples were withdrawn at different time intervals, filtered through millipore filter (0.45 µm), and measured for drug concentration spectrophotometrically at 360 nm using the same medium as blank.

Table (1): Characteristics of different tablet batches made using various binders.

Formula	The selected granule layer, prepared in tablet form
I	Upper layer of lactose granules made with 5% w/w P.V.P.
II	Third layer of lactose granules made with 5% w/w P.V.P.
III	Upper layer of lactose granules made with 15% w/w P.V.P.
IV	Third layer of lactose granules made with 15% w/w P.V.P.
V	Upper layer of lactose granules made with 0.5% w/w MC
VI	Third layer of lactose granules made with 0.5% w/w MC
VII	Upper layer of lactose granules made with 1.5% w/w MC
VIII	Third layer of lactose granules made with 1.5% w/w MC
IX	Upper layer of lactose granules made with 0.5% w/w HPMC
X	Third layer of lactose granules made with 0.5% w/w HPMC
XI	Upper layer of lactose granules made with 1.5% w/w HPMC
XII	Third layer of lactose granules made with 1.5% w/w HPMC
XIII	Upper layer of lactose granules made with 2.5% w/w gelatin
XIV	Third layer of lactose granules made with 2.5% w/w gelatin
XV	Upper layer of lactose granules made with 10% w/w gelatin
XVI	Third layer of lactose granules made with 10% w/w gelatin

RESULTS AND DISCUSSION

Following wet granulation and drying of the two formulations (A and B), it could be observed that, cyanocobalamin was no longer homogenously distributed throughout the four layers of the granulation bed.

Instead, cyanocobalamin migration has occurred from the two inner core layers (second and third layers) to the two surface layers (upper and base layers).

Table (3) shows that, for a specific binder, the values of migration coefficient had a descending order, on increasing the binder solution concentration or viscosity. For formula (A), dried at 50°C, the values of migration coefficient were 0.654, 0.54 and 0.292 for granules prepared with 5, 10 and 15 % w/w PVP, respectively. For MC, the values of migration coefficient were 0.678, 0.435 and 0.289 for granules prepared with 0.5, 1 and 1.5 % w/w MC, respectively. While, for HPMC, the values of migration coefficient were 0.692, 0.56 and 0.415 for granules prepared with 0.5, 1 and 1.5 % w/w HPMC respectively. Furthermore, in case of gelatin, the values of migration coefficient were found to be 0.685, 0.3 and 0.143 for granules prepared with 2.5, 5 and 10% w/w gelatin, respectively.

Table (2): The viscosity values of different concentrations of binder solutions.

Binder type	Binder concentration (% w/w)	Viscosity (mPa.s)
PVP	5	6.44
	10	11.5
	15	17.44
MC	0.5	15.6
	1	24.9
	1.5	69.8
HPMC	0.5	16.1
	1	35.7
	1.5	72.5
Gelatin	2.5	10.5
	5	13.9
	10	66.55

Table (3): Migration coefficient of cyanocobalamin using various binders and diluents, at different temperatures.

Binder type and conc. (%w/w)		Lactose (A)		Calcium phosphate (B)	
		50°C	70°C	50°C	70°C
PVP	5	0.654	0.548	0.948	0.853
	10	0.54	0.479	0.792	0.756
	15	0.292	0.29	0.688	0.632
MC	0.5	0.678	0.599	0.752	0.564
	1	0.435	0.415	0.543	0.476
	1.5	0.289	0.292	0.329	0.264
HPMC	0.5	0.692	0.647	0.933	0.862
	1	0.56	0.496	0.716	0.688
	1.5	0.415	0.365	0.483	0.345
Gelatin	2.5	0.685	0.678	0.9	0.819
	5	0.3	0.233	0.75	0.67
	10	0.143	0.093	0.36	0.195
Water		0.89	0.689	0.992	0.971

So, there is an obvious decrease in the values of migration coefficient with increasing the binder concentration and viscosity. These results are in agreement with that reported by Warren and Price,[4] who proved that, drug migration decreased with increasing binder solution viscosity, where increasing the concentration and therefore, the viscosity of PVP solution has been shown to slow the migration of propoxyphene hydrochloride in fixed bed of wet granules. This also was proved by Kiekens *et al.*,[5], who concluded that, the intragranular migration decreased as the granulating liquid viscosity increased. The viscosity of granulating fluids impedes the movement of moisture by increasing the fluid friction[6].

Spearman's rank correlation method was used to determine if a correlation exists between the extent of cyanocobalamin migration and increasing the binder solution viscosity. The values of r were; -0.6993 and -0.6758, -0.9066 and -0.8187 for formula A (dried at 50°C), Formula A (dried a. 70°C), formula B (dried at 50°C) and formula B (dried at 70°C), respectively, which are considered significantly different than zero. (When r value approaches 1, whatever the sign, there is a good correlation between the two studied variables. While, in case of r value equals zero, there is no correlation)

A significant negative correlation indicates that, there was an inverse relationship between the extent of cyanocobalamin migration and increasing the binder solution viscosity. Table (3) reveals that, the migration coefficient and hence the migration of the drug at 70°C is less than its analogue obtained at 50°C.

Newitt , Papadopoulos,[7] , Pietsch and Rumpf,[8] postulated that, solute migration on drying is reduced as the drying temperature is raised. They suggested that, at high temperatures, the flow of liquid through the granule cannot maintain the higher rate of drying at periphery and evaporation takes place from progressively further inside the granule. Travers,[9] stated that, solute migration is likely to be greatest when the evaporation rate is fairly slow at low rates of heat transfer. While, at higher rates, fluid friction will act to retard the moisture movement so that, the granule surface becomes dry at a stage when less overall movement has taken place.

From Table (3), it could be observed also that, formula B has a higher coefficient of migration than formula A, i.e. calcium phosphate shows a higher migration for cyanocobalamin. These results are in agreement with that reported by Warren & Price,[4] who concluded that, with calcium phosphate, more uniform layers did not occur until 600 cps binder solution was used; while with lactose, rather uniform layers were observed with 100 cps binder solution. This may be attributed to the greater amount of binder solution in formula B. Thus, with more solution to evaporate, more drug was carried to the surface[4, 10]. This may be due to the adsorption of the binding agents by the dibasic calcium phosphate, leaving a less viscous fluid to move by capillarity[11].

Tablet Evaluation

1. Uniformity of weight and thickness

Table (4) reveals that, all the batches of the prepared cyanocobalamin tablets showed good uniformity of weight and thickness.

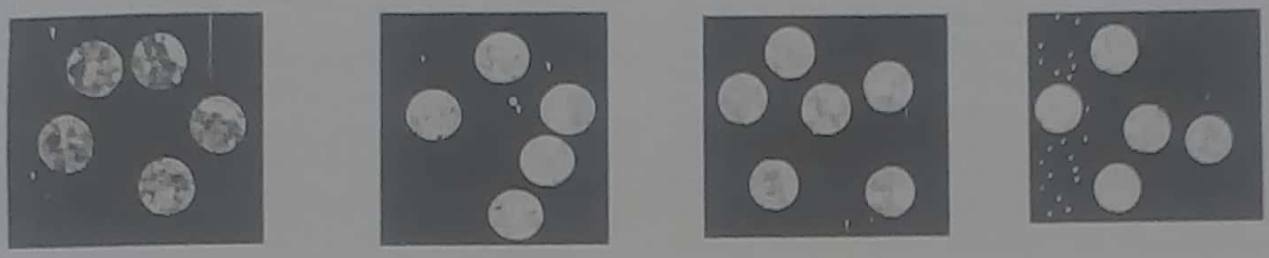
2. Friability

From Table (4), it could be observed that, all batches complied with the USP XXX requirements for the percent friability except for batches V, VI, VII, IX, and X since the loss percent values were > 1 %.

For PVP batches, the percent friability were 0.868% and 0.879% for batches I and II, respectively. While, for batches III and IV, the friability percent was 0.363% and 0.455%, respectively. Thus, increasing the binder solution concentration from 5 % w/w to 15 % w/w, led to a decrease in friability percentage.

The same pattern of results was obtained for the tablets prepared with the other binders. These results are in agreement with El- Sabbagh *et al.*,[12] who found that, increasing the concentration of a specific binder produced more strong granules which on compression, produced tablets of greatest hardness, lowest friability percentages, and highest disintegration time.

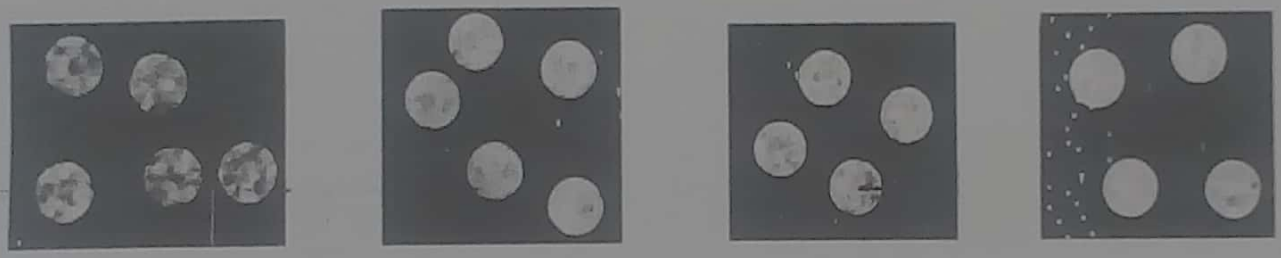
3. Visual inspection of the prepared tablets



(a) (b) (c) (d)

a. Upper layer made with 5 % PVP K_{25} (batch I).
b. Third layer made with 5 % PVP K_{25} (batch II).
c. Upper layer made with 15 % PVP K_{25} (batch III).
d. Third layer made with 15 % PVP K_{25} (batch IV).

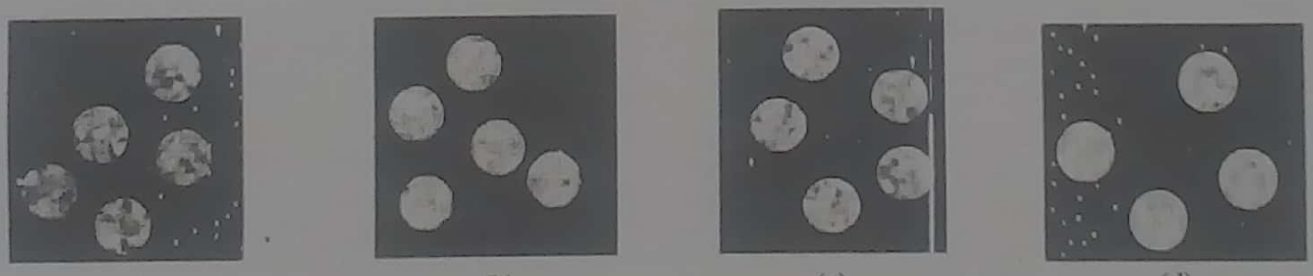
Fig. (2): Cyanocobalamin tablets prepared with PVP K_{25} binder



(a) (b) (c) (d)

a. Upper layer made with 0.5 % MC (batch V).
b. Third layer made with 0.5 % MC (batch VI).
c. Upper layer made with 1.5 % MC (batch VII).
d. Third layer made with 1.5 % MC (batch VIII).

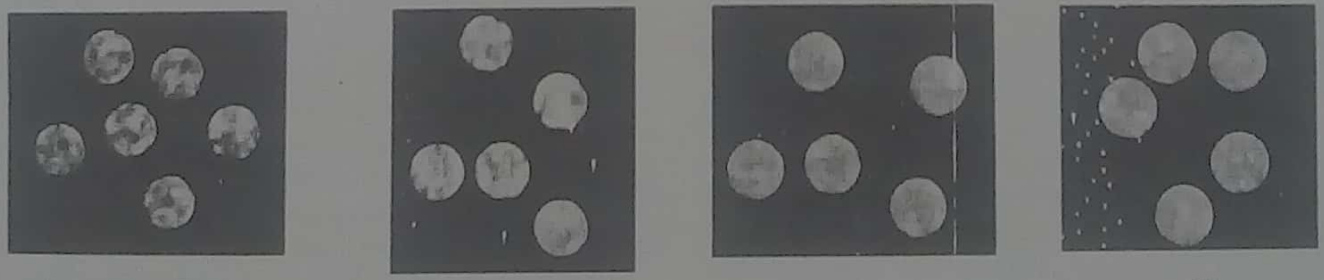
Fig. (3): Cyanocobalamin tablets prepared with MC binder



(a) (b) (c) (d)

a. Upper layer made with 0.5 % HPMC (batch IX).
b. Third layer made with 0.5 % HPMC (batch X).
c. Upper layer made with 1.5 % HPMC (batch XI).
d. Third layer made with 1.5 % HPMC (batch XII).

Fig. (4): Cyanocobalamin tablets prepared with HPMC binder



(a) (b) (c) (d)

a. Upper layer made with 2.5% gelatin (batch XIII).
b. Third layer made with 2.5 % gelatin (batch XIV).
c. Upper layer made with 10 % gelatin (batch XV).
d. Third layer made with 10 % gelatin (batch XVI).

Fig. (5): Cyanocobalamin tablets prepared with gelatin binder

4. Uniformity of drug content

From Table (4), it could be observed that, batch I (upper layer of lactose granules prepared with 5 % w/w PVP) showed a drug content of 213.53 µg per tablet (200 mg); while, batch II (third layer of lactose granules prepared with 5 % w/w PVP) had a value of 50.5 µg, with a difference of 163.03 µg between the two batches. This represents the high migration phenomenon of the drug to the upper layer upon drying of its wet granules, using a low viscous binder solution (5% PVP).

Drug content of batches III (upper layer of lactose granules prepared with 15 % w/w PVP) and IV (third layer of lactose granules prepared with 15 % w/w PVP) was 143.83 and 76.61 µg respectively, with a difference of 67.22 µg. The difference between the drug content of the two latter batches was decreased because drug migration was also decreased with increasing the binder concentration to 15% and hence, viscosity.

Also, Table (4), shows that, the same pattern has occurred with batches V (upper layer of lactose granules prepared with 0.5 % w/w MC) and VI (third layer of lactose granules prepared with 0.5 % w/w MC) which showed drug content values of 211.5 µg and 38.3 µg respectively, having a difference of 173.2 µg. Batches VII (upper layer of lactose granules prepared with 1.5 % w/w MC) and VIII (third layer of lactose granules prepared with 1.5 % w/w MC) showed drug content values of 142.35 µg and 87.4 µg respectively, having a difference of 54.95 µg.

While, the drug content values of batches IX (upper layer of lactose granules prepared with 0.5 % w/w HPMC) and X (third layer of lactose granules prepared with 0.5 % w/w HPMC) were 219.4 µg and 37.1 µg respectively. The difference in drug content between these two batches was 182.3 µg. On the other hand, the difference in drug content between batch XI (162.9 µg) and batch XII (59.6 µg) was 103.3 µg. Batches XI and XII refer to upper and third lactose granule layers prepared with 1.5 % w/w HPMC, respectively.

For granules made with different concentrations of gelatin, the drug content values of batches XIII (upper layer of lactose granules prepared with 2.5 % w/w gelatin) and XIV (third layer of lactose granules prepared with 2.5 % w/w gelatin) were 250.65 µg and 45.89 µg, respectively. The difference in drug content between the two batches was 204.76 µg. For batches XV (upper layer of lactose granules prepared with 10 % w/w gelatin) and XVI (third layer of lactose granules prepared with 10 % w/w gelatin), the values were 130.1 µg and 113.61 µg, respectively, with a difference in drug content of only 16.49 µg.

This indicates that, increasing the binder solution concentration, and hence viscosity, leads to a great decrease in drug migration. This drug migration was minimal in case of using 10 % w/w gelatin. So, the difference in drug content between the tablets made from the upper layer granules and the tablets made from the third layer granules was decreased to 16.49 µg.

5. Hardness

For each binder, the hardness values were found to increase with the increase in binder concentration. As illustrated in Table (4), in case of PVP, the hardness values were increased from 5.75 and 5 for batches I and II to 7.18 and 6.98 for batches III and IV, as the binder concentration was increased from 5 % w/w (batches I and II) to 15 % w/w (batches III and IV).

For MC, the hardness values were increased from 4.08 and 4.75 for batches V and VI (batches prepared with 0.5 % w/w MC) to 5.33 and 5.75 for batches VII and VIII (batches prepared with 1.5% w/w MC).

For HPMC, both batches IX and X which were prepared with 0.5 % w/w HPMC, had a hardness value of 5.75; while, on increasing the binder concentration to 1.5 % w/w, the values were raised to 6.75 and 6.73 for batches XI and XII, respectively.

In case of gelatin, the hardness value was 6.25 for both batches XIII and XIV (batches prepared with 2.5 % w/w gelatin), with an increase to 7.5 and 7.99 for batches XV and XVI, respectively (batches prepared with 10 % w/w gelatin).

Thus, 0.5 % w/w MC produced tablets with lowest hardness values, while 10 % w/w gelatin produced the hardest tablets in all batches. The high hardness values obtained with gelatin corresponds with its known property of producing hard tablets[13]. The hardness results confirm those of friability, i.e. as the hardness increased, the percent friability decreased and vice versa [14]. Generally, the strength of the granules, after drying, is mainly due to the development of solid bridges resulting from hardening of binders, crystallization of dissolved substances, or deposition of colloidal particles[15].

6. Disintegration time

From Table (4), it could be observed that, all batches comply with the USP XXVII requirements for disintegration.

From the same Table, it is shown that, batch I has a disintegration time of 8.23 min, which decreased to 4.6 min for batch II. This decrease in disintegration time may be attributed to the concurrent migration of PVP together with the drug to the surface layers of the granulation bed. Thus the upper layer of the granulation bed may contain higher percentage of PVP than the third layer which may account for the higher disintegration time of batch I than batch II. Polyvinyl pyrrolidone was reported to migrate to the surface layers upon drying of its wet granules [16]. The same pattern has occurred with higher PVP concentration, as batches III and IV had disintegrated after 13.53 min and 9.95 min., respectively.

Generally, this increase in the disintegration time of tablets prepared from the upper layers (batches I and III) than their analogues prepared from the third layer (batches II and IV) may be attributed to the deposition of fine crystals of the migrating solutes (binder and drug) in the upper layer, thus blocking the capillary network. Wells and Walker,[17] reported the impaired disintegration of aspirin tablets due to the deposition of fine crystals blocking the capillary network.

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Also, it could be observed that, batches corresponding to 0.5 % w/w MC had the least disintegration time values being 3 min and 2.87 min for batches V and VI, respectively. The disintegration time of the tablets containing various concentrations of MC is low at higher temperatures due to enhanced aqueous uptake [18]. Upon increasing MC concentration to 1.5 % w/w, the disintegration time was increased to 9.66 min and 9.83 min for batches VII and VIII, respectively.

Table (4) shows that, disintegration time values were 7.65, 7.1, 9.5, and 9.33 min for batches IX, X, XI, and XII respectively. So, increasing HPMC concentration from 0.5 to 1.5 % w/w resulted in an increase in disintegration time. While, the disintegration time values were 13 min and 10.3 min for batches XIII and XIV respectively and 20 min, 17 min for batches XV and XVI, respectively. Thus, increasing gelatin content, led to an increase in disintegration time. Esezobo and Pilpel,[19, 20] confirmed these results. These results, also, are in agreement with those reported by Jacob & Plein,[21] and Sakr *et al.*,[22] who demonstrated that, increasing gelatin content of tablets, leads to an increase in the mechanical strength, disintegration time, and dissolution time of the corresponding tablets. This is expected, since gelatin forms a dry film around the granules; this dried film must be rehydrated, since it forms a barrier to the diffusion of water and drug molecules. This will prolong the disintegration time and dissolution rate of the tablets[23].

Also, Davies and Gloor,[24] observed an increase in disintegration time of lactose tablets prepared with higher concentrations of binding agents and they attributed this to increased binding capacity of these granulating agents at higher concentrations.

7. *In vitro* drug release

Results of drug release from different formulations are illustrated in Figures: (6-9). Figure (6) shows the effect of PVP concentration on the drug release from different batches. It could be observed that, batch II (corresponding to third layer of lactose granules prepared with 5% w/w PVP), has a higher dissolution rate than batch I (corresponding to upper layer of lactose granules prepared with 5% w/w PVP), where the T_{90} values for both batches II and I were 8 and 18 min., respectively.

So batch II has slower dissolution rate, as indicated by the higher T_{90} value. This result may be attributed to the migration of the binder itself to the surface layers, i.e. from the second and third layers to the upper and base layers of granulation bed upon drying of wet granulations. This PVP migration was reported by Rubinstein & Ridgway,[16]. So, PVP, as well as cyanocobalamin, might be concentrated in the upper layer of granules, leaving the third layer deficient in both solutes. As a consequence, the tablets prepared from the upper layer (batch I) exhibited slower dissolution rate, longer disintegration time, and of course higher drug content than the tablets prepared from the third layer (batch II). Upon increasing PVP concentration to 15 % w/w, the rate of drug release was decreased than tablets containing 5% PVP.

Table (4): Physical properties of cyanocobalamin tablets, prepared with different concentrations of binders.

Batch No.	Weight (mg) Mean ± SD	Drug content (µg) Mean ± SD	Thickness (mm) Mean ± SD	% Friability	Hardness (Kg) Mean ± SD	Disintegration time (min.)	Dissolution rate (T_{90}) (min.)
I	200.4 ± 1.1	213.53 ± 2.4	2.18 ± 0.016	0.868	5.75 ± 0.56	8 23	18
II	202.4 ± 0.89	50.5 ± 1.5	2.18 ± 0.016	0.879	5 ± 0.98	4.6	8
III	202.4 ± 1.34	143.83 ± 1.98	2.17 ± 0.015	0.363	7.18 ± 0.74	13.53	28
IV	201.9 ± 1.8	76.61 ± 2.5	2.16 ± 0.014	0.455	6.98 ± 1.1	9.95	26
V	200.4 ± 1.12	211.5 ± 2.12	2.11 ± 0.01	2.2	4.08 ± 0.96	3	12
VI	199 ± 1.3	38.3 ± 3.1	2.11 ± 0.01	1.8	4.75 ± 0.79	2.87	14
VII	200.5 ± 1.2	142.35 ± 2.19	2.12 ± 0.012	1.23	5.33 ± 0.85	9.66	37
VIII	201.3 ± 1.01	87.4 ± 1.7	2.116 ± 0.015	0.984	5.75 ± 0 77	9.83	36
IX	198.8 ± 1.6	219.4 ± 1.05	2.1 ± 0.02	1.02	5.75 ± 0.74	7.65	20
X	198.2 ± 1.4	37.1 ± 0.56	2.09 ± 0.02	1.3	5.75 ± 0.63	7.1	15
XI	199.4 ± 1.3	162.9 ± 2.4	2.13 ± 0.01	0.587	6.75 ± 1.05	9.5	30
XII	201.4 ± 1.8	59.6 ± 0.83	2.16 ± 0.011	0.621	6.73 ± 0.92	9.33	28
XIII	199 ± 1.58	250.65 ± 2.32	2.15 ± 0.01	0.559	6.25 ± 1.2	13	48
XIV	200.8 ± 1.3	45.89 ± 1.85	2.15 ± 0.02	0.467	6.25 ± 0.99	10.9	42
XV	200.1 ± 1.2	130.1 ± 2.5	2.15 ± 0.01	0.23	7.5 ± 1.1	20	75
XVI	201.8 ± 1.6	113.61 ± 1.69	2.15 ± 0.02	0.158	7.99 ± 1.08	17	72

Also, the obtained results reveal that, the batches III and IV have lower dissolution rate than batches I and II, where the T_{90} values were 28 and 26 min. for both batches III and IV, respectively. Zubair *et al.*,[23] explained why the increasing in the binder concentration, increases markedly the disintegration and dissolution times of the corresponding tablets. This is because, binders are forced into the interparticular spaces, thereby increasing the area of contact between particles, leading to the formation of additional solid bonds.

It is also suggested that, at lower compression forces, dissolution rates are related to the structure and crushing characteristics of the granules, and, therefore, to the concentration of PVP binder[23].

Chalmers and Elworthy,[26] found that, increasing the concentration of PVP as binder solution resulted in a decrease in the rate of tablet dissolution. They attributed this to the heavier coating of the powder particles with PVP at high concentrations which may act by slowing the rate at which invading water reaches the surface of the powder particles, and slowing diffusion away from the surface of the drug, due to higher viscosity of PVP solutions compared with that of pure water.

Figure (7) illustrates the effect of MC on the dissolution rate of cyanocobalamin from its tablets. It could be noticed that, both batches, V and VI exhibit rapid dissolution rate (T_{90} = 12 and 14 min., respectively). This may be due to the use of lower binder concentration (0.5 % w/w). However, on using 1.5 % w/w MC as a binder solution, the rate of drug release was lowered as exhibited by batches VII and VIII which had T_{90} values of 37 and 36 min., respectively.

As shown in Figure (8), the same pattern was obtained with HPMC, where both batches IX and X (corresponding to tablets prepared from upper and third layers of 0.5 % w/w HPMC granulations, respectively) showed a higher dissolution rate (T_{90} = 20 and 15 min., respectively) than batches XI and XII, which were prepared using 1.5 % w/w HPMC (T_{90} = 30 and 28 min., respectively).

Figure (9) shows that, the tablets prepared with gelatin binder solution have prolonged dissolution rate with respect to all the other prepared batches. From the same figure, it could be seen that, both batches: XIII and XIV (corresponding to tablets prepared from upper and third layers of 2.5 % w/w gelatin granulations, respectively) have a higher dissolution rate than batches XV and XVI which are prepared with 10 % w/w gelatin. The T_{90} values were 48 and 42 min. for batches XIII and XIV. While, for batches XV and XVI, it was increased to 75 and 72 min. respectively. These results are in agreement with those reported by Esezobo and Pilpel,[19].

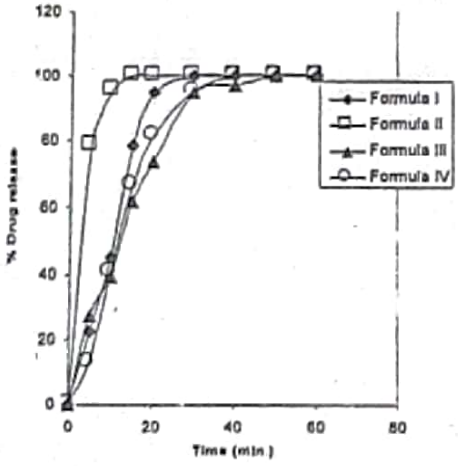

Fig. (6): Effect of PVP concentration on cyanocobalamin release from tablets corresponding to different layers of granulation bed.

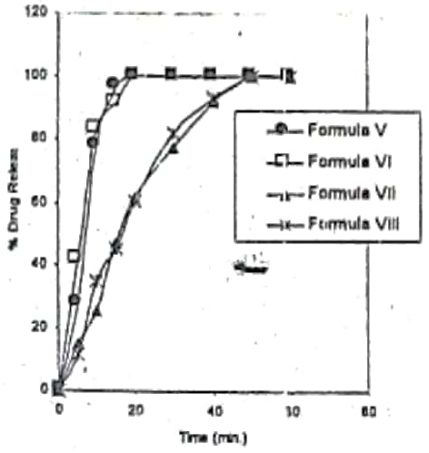

Fig. (7): Effect of MC concentration on cyanocobalamin release from tablets corresponding to different layers of granulation bed.

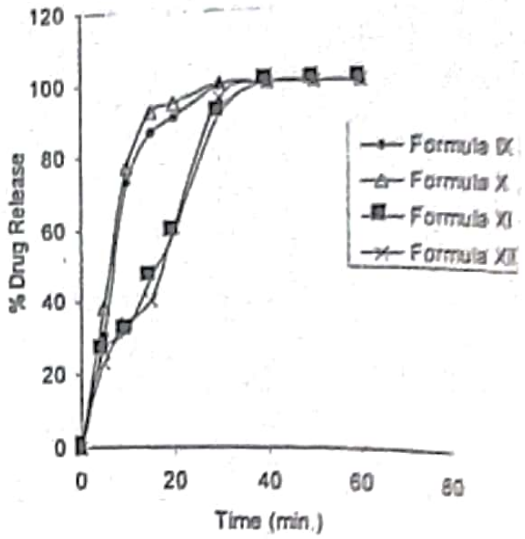

Fig. (8): Effect of HPMC concentration on cyanocobalamin release from tablets corresponding to different layers of granulation bed.

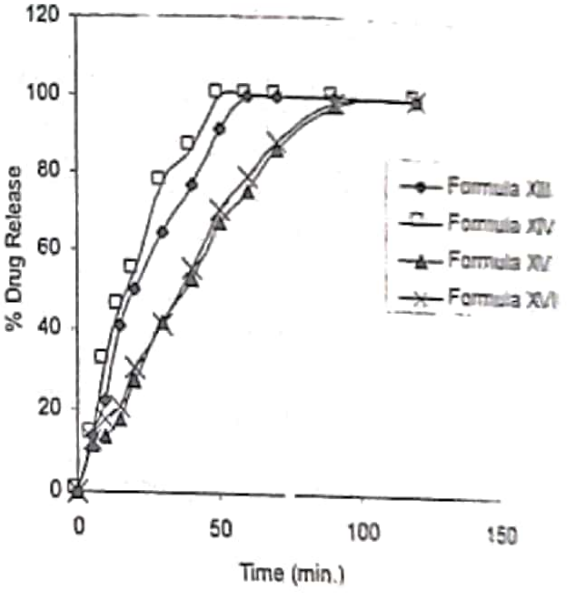

Fig. (9): Effect of gelatin concentration on cyanocobalamin release from tablets corresponding to different layers of granulation bed.

CONCLUSION

It could be concluded that, the migration of the colored low dose drugs, e.g., cyanocobalamin upon drying of their wet granules represents a serious problem in the industry, concerning the drug uniformity within the prepared tablets, and so, the mottling and dose uniformity. This problem can be solved by the proper choice of the diluent type, binder type and concentration, and drying temperature during the drying of the wet granules.

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تأثير تصنيع الأقراص على هجرة فيتامين ب١ من الحبيبات أثناء تجفيفها

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إن هجرة الأدوية القابلة لذوبان فى الماء وذات الجرعة المنخفضة أو المواد الملونة أثناء تجفيف الحبيبات الرطبة، قد تؤدى إلى حركة المادة الفعالة الذائبة من حبيبة إلى أخرى مما يتسبب في سوء توزيع المادة الفعالة أو المادة الملونة فى الحبيبات ومن ثم فى الأقراص المصنعة منها. و نتيجة لذلك، قد يحدث إختلاف كبير في جرعة الدواء من قرص إلى آخر حتى في نفس تشغيلة الأقراص الواحدة وخاصة في حالة الأدوية ذات الجرعة الصغيرة وذات الفاعلية العالية. أما هجرة اللون فقد تتسبب في الحصول على أقراص غير مقبولة الشكل.

فى هذه الدراسة، تم تحضير حبيبات مختلفة تحتوي على السيانوكوبالامين بإستخدام سوائط مختلفة (الاكتوز أحادى الماء وفوسفات الكالسيوم ثنائي القاعدة)، ومحاليل مائية لروابط متنوعة وهي عديد فينيل البيروليدون كد، (٥ و ١٠ و١٥ %) و سيليولوز الميثيل (٠,٥ و ١ و١,٥ %) وهيدروكسى بروبيل ميثيل السيليولوز (٠,٥ و ١ و١,٥ %) و الجيلاتين (٢,٥ و ٥ و ١٠ %) . ثم بعد ذلك تم تجفيف الحبيبات الرطبة في خلية تجفيف خاصة عند درجتي حرارة ٥٠ °م و٧٠ °م، ثم حساب قيمة معامل الهجرة للدواء فى الحبيبات الجافة. وتلى ذلك كبس بعض الطبقات المختارة من هذه الحبيبات الجافة فى صورة أقراص وتقييمها فيزيائيا من حيث المظهر العام، محتوى الدواء، الوزن، الصلابة، الهشاشة، التفتت ومعدل الانطلاق المعملي للدواء.

اوضحت النتائج أن هجرة الدواء كانت أعلى في حالة الحبيبات المحضرة باستخدام فوسفات الكالسيوم ثنائي القاعدة عن تلك المحضرة باستعمال اللاكتوز وأن زيادة تركيز الرابط وبالتالى زيادة لزوجته تؤدى إلى تقليل هجرة الدواء. كما أن هجرة الدواء حدثت بدرجة أقل عند تجفيف الحبيبات عند درجة حرارة ٧٠ °م. كما تبين أيضا أن الحبيبات المحضرة باستخدام اللاكتوز و١٠ % و/ و جيلاتين و التي تم تجفيفها عند درجة حرارة ٧٠ °م قد أظهرت أقل هجرة للسيانوكوبالامين من الحبيبات (معامل الهجرة = ٠,٠٩٣).

وقد اتضح أيضا من النتائج أن الأقراص المصنعة من الحبيبات المحضرة بمحاليل روابط ذات لزوجة منخفضة كانت ذات مظهر مبقع وغير مقبول. بينما إنعدمت هذه الظاهرة مع إستخدام المحاليل ذات اللزوجة العالية. كما أن زيادة تركيز الرابط أدت إلى تقليل معدل إنطلاق الدواء من الأقراص. و أن الأقراص المحضرة باستعمال ١٠ % جيلاتين قد أظهرت توزيعاً متجانساً للدواء ولكن كان لها أقل معدل إذابة و أعلى وقت تفتت مقارنة بالأقراص الأخرى. أما الأقراص المحضرة من حبيبات باستعمال ٠,٥ % ميثيل السيليولوز كانت لها نسبة هشاشة عالية (٢,٢ %) وأقل صلابة (٤,٠٨) وأقل وقت للتفتت (٢,٨٧ دقيقة). كما أثبتت الدراسة أيضا هجرة الدواء و الرابط عديد فينيل البيروليدون إلى الطبقات السطحية للحبيبات مما أدى إلى اختلاف في معدل الانطلاق المعملي للدواء.