Formulation and *In Vitro* Evaluation of vitamin A palmitate tablets containing Carbopol 971

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Citation

Abstract
The sustained release (SR) properties of vitamin A palmitate (VAP) from tablet matrices formulated with a poly (acrylic) acid polymer, Carbopol 971 (CP 971) were investigated *in vitro*. Formulations containing Carbopol 971 at concentrations of 10, 20, 30 and 40 % w/w were wet granulated using ethanol 95% v/v. Micromeritic evaluation of the dried granules, tablet characterization and drug dissolution studies were done in 0.05 M phosphate buffer(containing Triton X – 100®), simulated intestinal fluid (SIF) and simulated gastric fluid (SGF) without enzymes. Results obtained showed a burst release of VAP within 60 min (1 h) of the test followed by a slow retardation of VAP release over the next 7 h as the concentration of the CP 971 increased indicating SR activity. Dissolution of vitamin A palmitate was higher in the 0.05 M phosphate buffer than in SIF and SGF. The release kinetics involved mixed order while release mechanism was dominantly diffusion controlled (Fickian or Case I).

1. Introduction
Oral administration of drugs using controlled release formulations is a popular concept which has attracted the attention of formulators within the last four decades (Ofoefule and Chukwu,1999; Ofoefule and Amanambu, 1998). Administration of such formulations result in the gradual release of the active drug in the gastro-intestinal tract (GIT) without frequent dosing( Jambhakar, 2009). They are preferred to conventional dosage forms because of some advantages such as reductions in patient non compliance, fluctuation of circulating drug levels, gastro intestinal irritations, and elimination of the patient staying awake or being woken up at night to take his/her medications. Drugs for sustained release formulations should have a relatively short biologic half life, a fair margin of safety (non toxicity), uniform absorption from the gastro-intestinal tract (GIT) and should be used for the treatment of chronic conditions (Apu et al, 2009). Vitamin A palmitate has a biologic half life of 1.9 h (De Clerk et al, 1998), is well absorbed from the GIT, is essential for vision, dental development, growth and reproduction (Fawsi et al 2000, USP 32 2009). Its deficiency causes nyctalopia, xerophtalmia, diminished...

2. Materials and Method

2.1. Materials

Vitamin A palmitate (Evans Nigeria Plc), Carbopol 971 (G.F. Goodrich, Ohio), potassium dihydrogen phosphate (Aldrich, USA), sodium ascorbate (SKG Pharma, Nigeria Plc), Triton X-100®, ethanol, stearic acid (Sigma Chem Coy, USA), talc (May and Baker, England), lactose and sodium chloride (BDH, Poole, England).

2.2. Method

2.2.1. Preparation of granules

Accurate quantities of lactose, VAP, and CP 971 (Table 1) to yield a batch size of 100 tablets of 300 mg each were weighed into a Wedgewood mortar and triturated for 20 min using the geometric dilution method. One batch (batch 1) did not contain CP 971 and served as the control. The wet granulation method was used and wet massing was done with 95% v/v ethanol. Granules were formed by passing the wet mass through a 1.7 mm stainless steel sieve. The resultant granules were dried at 30°C in an oven (Memmert®, GmbH, Germany), screened through a 1.0 mm stainless steel sieve and stored in amber colored bottles. All granulations were done under subdued sunlight.

3. Evaluation of Granules

3.1. Flow Rate and Angle of Repose

The fixed funnel and free standing cone method were used in the determination of angle of repose. A 10 g quantity of VAP granule was poured into a glass funnel with orifice and base diameter of 1.10 cm and 5.50 cm respectively. The funnel was fixed at a height of 15.00 cm above a flat surface.

The time of flow of the granules, the diameter and height of the granules heap formed were determined. The flow rate and the tangent of the angle of the granule heap were calculated from Equations 1 and 2 (Okorie and Nwachukwu, 2013).

Flow rate (F.R.) = M / F.T. (sec)                                          (1)

Angle of repose (θ) = tan⁻¹(h/r)                                          (2)

Where M = mass of granules, F.T. = flow time of granules and h = height of granule heap and r = radius of granule heap.

3.2. Bulk and Tapped Densities

The bulk and tapped densities of VAP granules were determined using a dry 100 mL glass measuring cylinder kept on a flat table surface. A 10 g quantity of VAP granules were freely poured into the dry 100 mL measuring cylinder and the volume, Vb noted. The cylinder was mechanically tapped on the flat table surface until no further decrease in volume Vt was observed. The bulk and tapped densities were calculated as a ratio of the granule mass and the respective volumes from Equations 3 and 4

Bulk density (Db) = M / Vb                                           (3)

Tapped density (Dt) = M / Vt                                         (4)

Where M = mass of granules.

3.3. Hausner’s Quotient and Carr’s Index

Hausner’s quotient and Carr’s index were calculated from equations 5 and 6 (Ganesh et al, 2006)

Hausner’s quotient (HQ) = Dt / Db                                       (5)

Carr’s index (CI) = (1 – Db / Dt) x 100                                 (6)

4. Compression of Tablets

Prior to compression 0.5% w/w of talc and 1.00 % w/w of stearic acid were added to each granule batch. The granules, talc and stearic acid were mixed in the amber colored glass bottle for 10 min. Tablet compression was done with a single punch tablet press model F – 3 (Manesty®, England) fitted with a set of 9.50 mm biconcave punches to a target weight of 300 ± 15 mg. Compression was done at a fixed pressure unit of the machine.

4.1. Evaluation of Tablets

Compressed tablets were evaluated for weight variation,
friability, crushing strength and dissolution profile studies 24 h after compression.

4.2. Weight Variation

Twenty tablets randomly selected from each tablet batch were weighed individually and collectively using an Adventurer® analytical balance according to the British Pharmacopoeia, BP method (BP 2009). The mean deviation and coefficient of variation were calculated. The acceptance or rejection criteria for each tablet is as stipulated in the BP 2009.

4.3. Hardness Test

Ten tablets randomly selected from each tablet batch were tested on an electronic hardness tester, model TBH 28 W (Erweka® GmbH, Germany) and the value recorded in Kg/f units. The mean crushing strength and standard deviation were determined for each batch (Banker and Anderson, 1999).

4.4. Friability Test

Ten tablets randomly selected from each tablet batch were tested on an electronic twin drum friability tester, model TAR 200 (Erweka®, GmbH, Germany) programmed to revolve at 25 rpm for 4 min. Percentage loss in weight for each batch was calculated from equation 7

\[ B = 100 \left\{ 1 - \frac{W}{W_o} \right\} \]  

Where \( B \) = friability or % loss in weight, \( W_o \) = initial tablet weight and \( W \) = final tablet weight.

4.5. Assay of Tablets

Twenty tablets randomly selected from each tablet batch were collectively weighed using an Adventurer® analytical balance. The samples were dispersed in 80 mL of the phosphate buffer, filtered and the volume made up to 100 mL with an equal amount of dissolution medium maintained at the same temperature. Withdrawn samples were filtered and the filtrate assayed spectrophotometrically at 323 nm for SIF and 0.05 M phosphate buffer and at 321 nm for SGF. The release data for each dissolution medium was analyzed by fitting data into the following release kinetics and release models.

4.7. Zero order

\[ C = K_o t \]  

Where \( K \) = rate constant and \( t \) = time.

First order

\[ \log C_t = \log C_o - K_1 t / 2.303 \]  

Where \( C_t = \% \) drug remaining, \( C_o = initial \) drug concentration, \( K_1 = First \) order rate constant and \( t = time. \)

4.8. Higuchi Square Root Kinetics

\[ Q = K_H t^{1/2} \]  

Where \( Q = \% \) drug remaining, \( K_H = constant \) reflecting design variables of the system and \( t = time. \)

4.9. Korsmeyer- Peppas Model

\[ M_t / M_i = Kt^n \]  

Where \( M_t / M_i = fraction \) of drug released at time, \( t \), \( K = rate \) constant while \( n \) characterizes the different mechanisms of release.

Statistical evaluation of data was done using Graph Pad Prism® 5.04

5. Results

Tables 2 and 3 show the micromeritic properties of the granules and the in vitro tablet properties respectively.

<table>
<thead>
<tr>
<th>Batch</th>
<th>Flow rate ((\text{SD ± (g/s)})^a)</th>
<th>Angle of repose ((\text{SD ± (%))}^a)</th>
<th>Bulk Density (\text{(SD ± (g/ml))}^a)</th>
<th>Tapped Density (\pm\text{SD}^a)</th>
<th>Hauser’s Compressibility Density quotient</th>
<th>Compressibility Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.00 ± 0.40</td>
<td>26.76 ± 0.61</td>
<td>0.43 ± 0.00</td>
<td>0.52 ±0.00</td>
<td>1.20 ± 0.00</td>
<td>17.30 ± 0.00</td>
</tr>
<tr>
<td>2</td>
<td>8.00 ± 0.00</td>
<td>27.60 ± 0.86</td>
<td>0.46 ± 0.00</td>
<td>0.52 ±0.00</td>
<td>1.13 ± 0.00</td>
<td>11.15 ± 0.00</td>
</tr>
<tr>
<td>3</td>
<td>8.00 ± 0.00</td>
<td>26.90 ± 3.55</td>
<td>0.46 ± 0.00</td>
<td>0.52 ±0.00</td>
<td>1.13 ± 0.00</td>
<td>11.50 ± 0.00</td>
</tr>
<tr>
<td>4</td>
<td>8.16 ± 0.23</td>
<td>28.80 ± 0.72</td>
<td>0.46 ± 0.00</td>
<td>0.54 ±0.00</td>
<td>1.17 ± 0.00</td>
<td>14.80 ± 0.00</td>
</tr>
<tr>
<td>5</td>
<td>9.00 ± 0.28</td>
<td>29.86 ± 0.74</td>
<td>0.47 ± 0.00</td>
<td>0.54 ±0.00</td>
<td>1.14 ± 0.00</td>
<td>12.50 ± 0.00</td>
</tr>
</tbody>
</table>

*\(n = 3\) where \(n\) is the sampling size.
**5.1. Content of Active Ingredient**

Batches of the tablets containing 0 to 40% w/w of CP 971 contained 93.38 ± 0.23 %, 96.51 ± 0.13 %, 98.19 ± 0.22 %, 96.42 ± 4.12 % and 97.05 ± 0.13 % of the VAP respectively.

**5.2. Dissolution Profile**

Figures 1 and 2 show the dissolution profiles of vitamin A palmitate tablets in 0.05 M phosphate buffer and in the different media with varying pH (0.05 M phosphate, SGF and SIF) respectively.

![Fig. 1. Dissolution profile of Vitamin A palmitate tablets in 0.05 M Phosphate buffer](image1)

![Fig. 2. Dissolution profile of Vitamin A palmitate in 0.05 M Phosphate buffer, SIF and SGF](image2)

<table>
<thead>
<tr>
<th>Batch</th>
<th>Uniformity of weight (mg ± CV (%))</th>
<th>Hardness test (SD ± (Kg/F))</th>
<th>Friability (SD ± (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>291.05 ± 1.47</td>
<td>6.75 ± 1.10</td>
<td>0.70 ± 0.00</td>
</tr>
<tr>
<td>2</td>
<td>294.55 ± 2.02</td>
<td>7.75 ± 0.64</td>
<td>0.52 ± 0.01</td>
</tr>
<tr>
<td>3</td>
<td>293.15 ± 1.79</td>
<td>8.40 ± 0.49</td>
<td>0.15 ± 0.00</td>
</tr>
<tr>
<td>4</td>
<td>297.60 ± 2.51</td>
<td>9.05 ± 0.68</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>5</td>
<td>301.40 ± 1.84</td>
<td>11.70 ± 2.74</td>
<td>0.00 ± 0.00</td>
</tr>
</tbody>
</table>

*n = 20 and **n = 10 where *n and **n = number of samples.

**Table 3. In vitro vitamin A tablet evaluation results**

![Table 4. T_m and C_max of vitamin A palmitate tablets](image3)

**6. Discussion**

**6.1. Granules Evaluation**

The flow rate values were between 8.00 ± 0.40 g/s to 9.00 ± 0.28 g/s, angle of repose ranged from 26.76 ± 0.61° to 29.86 ± 0.74°, bulk density 0.43 ± 0.00 to 0.47 ± 0.00 g/mL, tapped density 0.52 ± 0.00 to 0.54 ± 0.00. Hausner’s quotient ≤ 1.2 and Carr’s index 11.15 ± 0.00 to 17.30 ± 0.00 %. These flow indices indicate that the granules would flow well during tabletting operations. Flow properties generally increased with increased polymer concentration.

**6.2. Tablet Properties**

Some of the in vitro tablet properties are shown in Table 3. The tablets were found to be intact when visually examined. The tablets coefficient of variation ranged from 1.47 to 2.51 %. These values are within variations considered adequate for uncoated tablets with weight not less than 250 mg (Banker, 1991). The hardness of the tablets ranged from 6.75 ± 1.10 to 11.70 ± 2.74 Kg/f. These values increased as the CP 971 concentration increased and were within acceptable values for conventional compressed tablets (Ofoefule,2002, Osadobe,2004). The friability values were < 1.00 %. Although there are no official specifications for friability, conventionally uncoated tablets with friability of ≤ 1.00 % are considered strong enough to withstand objectionable abrasion levels during handling and transportation (BP 2011).

**6.3. Content of Active Ingredient**
The tablet batches containing 10% to 40% w/w of the polymer complied with USP assay requirements for content of active ingredient in respect of vitamin A palmitate which stipulates not < 95 % or > 125 % of the labeled amount (United States Pharmacopeia [USP] 32, 2009).

6.4. Drug Release Studies

In hydrophilic polymeric matrices, the carrier on the surface of the matrix initially hydrates during dissolution to generate an outer viscous layer. Sequentially matrix bulk hydration, swelling and erosion occurs. The overall dissolution rate and eventual amount of drug available is controlled by the rate of matrix swelling, drug diffusion through the gel layer and/matrix erosion (Ofoefule et al 2000, Sinha and Roberts 2012, Ofoefule and Chukwu, 2000). The dissolution profile of VAP tablets are shown in Figure 1. The control batch that did not contain CP 971 as should be expected exhibited the fastest release. There was an initial fast release (burst release) of the drug from all the batches within the first 60 min (1 h) and thereafter a gradual slow release followed. There was more than 50 % release of the drug content from all batches within 480 min (8 h) release period (Table 4). The time taken for 50% of VAP to be released (t50) from the different polymer concentrations (10 %, 20 %, 30 % and 40 % w/w) were 180, 220, 340 and 380 min respectively in 0.05 M phosphate buffer. The effect of pH on the release of VAP is shown in Figure 2. Drug release was higher in the alkaline media of 0.05 M phosphate buffer and SIF than the acidic medium of SGF. The presence of Triton X - 100®, a hydrophilic surfactant could have aided the increased release of VAP in the phosphate buffer. The addition of surfactants to a dissolution medium has been reported to increase the dissolution of powder drugs and their tablets (Honary et al. 2007).Surfactants such as Triton X -100® can enhance the dissolution of a poorly soluble drug in a tablet by a reduction of the interfacial tension and micelle formation (Remya et al.,2010). At a critical micelle concentration, the surfactant forms micelles which arise from the aggregation of molecules containing distinct regions of hydrophilic characters and which trap the drug molecules thereby increasing their solubility (Florence and Attwood, 1989) and enhancing a greater release in the medium.

6.5. Kinetics and Mechanism of Drug Release

The mechanism of drug diffusion from polymeric matrices can be classified as Fickian (Case I) or First order if n = 0.5, non Fickian or anomalous if 0.5 < n < 1.0, Zero order (Case II ) if n = 1, and Super Case II if n > 1.0 (Sood and Panchannula, 1998). The kinetics and mechanism of release of VAP is shown in Table 5. All the batches containing CP 971 exhibited mixed order kinetics. At 10 % to 30 % w/w, First order kinetic was dominant while at 40 % w/w Higuchi square root kinetic was dominant. The mechanism of drug release at 10% and 40% w/w CP 971 was Non Fickian (anomalous) while at 30% w/w , the release was Fickian (Case I ) or diffusion controlled. In SGF and SIF, the release kinetics involved all the three kinetic models with their order of involvement being Higuchi kinetic model > First order > Zero order. The mechanism of release in SGF and SIF was dominantly Case I ( Fickian ). Statistical analysis showed significant differences in the release (p < 0.05) at 60, 180, 240, 300, 360, 420 and 480 minutes while an insignificant difference in release was observed at 120 min in all three media used (0.05M phosphate buffer, SGF and SIF). The insignificant difference in release at 120 min may have resulted from the activity of the viscous gel layer formed on the periphery upon wetting of the tablet which may be thick, strong and very viscous at this sampling time. Drug release from hydrogels has been reported to be controlled by the degree of crosslinking (Zarzycki et al., 2010).

7. Conclusion

Vitamin A palmitate granules showed good flow properties based on their micromeric properties and the tablets had good hardness, and friability values which indicates that they are strong enough to resist objectionable abrasion and shock stresses during transportation and handling. All tablet batches had adequate weight variation in accordance with compendial specifications. There was more than 50% drug release for all the batches in all three dissolution media used. Vitamin A palmitate release was more in the alkaline media (buffers) than acidic medium. The release kinetic was mixed order while release mechanism was diffusion controlled (Fickian) in all three media. A significant difference in drug release (p < 0.05) was also observed at all sampling times except at 120 min in all three media at 30 % w/w CP 971. This study shows that CP 971 is a good matrix for the formulation of sustained release tablets of VAP and it is suggested that the polymer be used at 20 % or 30 % w/w.

Acknowledgement

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