In-vivo evaluation of clindamycin release from glyceryl monooleate-alginate microspheres by NIR spectroscopy

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ABSTRACT

The purpose of this study was to use near-infrared (NIR) transmission spectroscopic technique to determine clindamycin plasma concentration after oral administration of clindamycin loaded GMO-alginate microspheres using rabbits as animal models. Lyophilized clindamycin–plasma standard samples at a concentration range of 0.001–10 μg/ml were prepared and analyzed by NIR and HPLC as a reference method. NIR calibration model was developed with partial least square (PLS) regression analysis. Then, a single dose in-vivo evaluation was carried out and clindamycin–plasma concentration was estimated by NIR. Over 24 h time period, the pharmacokinetic parameters of clindamycin were calculated for the clindamycin loaded GMO-alginate microspheres (F3) and alginate microspheres (F2), and compared with the plain drug (F1). PLS calibration model with 7–principal components (PC), and spectral range shows a good correlation between HPLC and NIR values with root mean square error of cross validation (RMSECV), root mean square error of prediction (RMSEP), and calibration coefficient (R²) values of 0.245, 1.164, and 0.9753, respectively, which suggests that NIR transmission technique can be used for drug-plasma analysis without any extraction procedure. F3 microspheres exhibited controlled and prolonged absorption Tmax of 4.0 vs. 1.0 and 0.5 h; Cmax of 2.37 ± 0.3 vs. 3.81 ± 0.8 and 5.43 ± 0.7 μg/ml for F2 and F1, respectively. These results suggest that the combination of GMO and alginate (1:4 w/w) could be successfully employed for once daily clindamycin microspheres formulation which confirmed by low Cmax and high Tmax values.

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1. Introduction

Clindamycin [7(S)-chloro-7-deoxylincomycin] (Fig. 1) is a water-soluble antibiotic that is highly effective against Gram-positive and Gram-negative anaerobic pathogens, as well as Gram-positive aerobes. It is synthesized from microbially fermented lincomycin by replacing a hydroxyl group at the 7-position of lincomycin by a chlorine group which significantly increases its activity (Sheikhhoie and Farhadi, 2010). Clindamycin primary effect is exerted by its binding to the 50S ribosomal subunit and the consequent inhibition of bacterial protein synthesis (VuKomanovic et al., 2011). Clindamycin is mainly used in the treatment of serious respiratory tract infection, serious skin, and soft tissue infections, septicemia, intra-abdominal infections and infections of the female pelvis and genital tract caused by susceptible anaerobic bacteria (Platzker and White, 2006). The biological half-life of clindamycin is about 2.9 h, thus necessitating frequent administration (3–4 times a day) to maintain constant therapeutic drug levels (Piasance et al., 1989). This frequent administration could affect the compliance, thus the efficacy of the antibiotic. A sustained release formulation, such as biodegradable microspheres, could decrease the frequency of drug administration, thus improve the compliance.

Calcium alginate matrix is one of the commonly used biodegradable microspheres, but the resulting calcium alginate bead is usually very permeable, making it very difficult to control water soluble drug release for a prolonged period of time in physiologic salt concentration (Ghosal and Ray, 2011). In the presence of monovalent (e.g., sodium) salts, insoluble calcium alginate gets converted into a soluble form (sodium alginate), resulting in rapid disintegration of
the delivery system and drug release (Moebus et al., 2009). This problem can be minimized by mixing alginate with glyceryl mono-
oleate (GMO). Where in a previous study, a new kind of micro-
particle was prepared based on GMO dispersions and alginate using emulsification and cross-linking method to provide prolonged in-
vitro release of the water soluble clindamycin. The resulted particles had a uniform structure, a satisfactory entrainment efficiency, and accepted in-vitro sustained release properties (>20 h) encouraging further in vivo investigation (Mohamed et al., 2014).

Clindamycin distributes widely throughout the body with a high degrees of protein binding. The level of protein binding in humans ranges from 62% to 94% and is mainly excreted into urine and bile (Muller et al., 2010). A number of analytical methods have been reported for measuring clindamycin in bulk drugs and formulations as well as in biological fluids and tissue or cell homogenates or organ extracts. Most of these methods are either non-specific, time-and-reagent consuming or involve the using a couple of columns and two mobile phases to extract clindamycin from human plasma samples (Na-Bangchang et al., 2006).

Near-infrared (NIR) spectroscopy technique has been widely used as a fast, low cost and non-destructive analysis of biological materials including quantitative determination of drugs in plasma. The clearest advantages involve that no specific reagents are required, and automated-repetitive analyses can be easily carried out. Powerful chemometric algorithms and software packages have emerged in parallel with the new generation of analytical IR spectrometers, and thus new applications emerge continually (Yu and Xiang, 2008). The wave number of NIR is from 4000 cm$^{-1}$ to 12,500 cm$^{-1}$, which mainly covers overtones and combinations of molecular vibrations for functional groups involving hydrogen atom such as C–H, N–H, O–H, and S–H gups. Based on the molecular vibrations, the NIR frequency range can be divided into four ranges: combination region (4000–4900 cm$^{-1}$), first combination overtone (4900–7100 cm$^{-1}$), second combination overtone (7100–10,000 cm$^{-1}$), and third overtone (10,000–12,500 cm$^{-1}$) (Wu et al., 2014). Usually, multivariate calibration needs to be employed for modelling spectral data and establishing the relationship of the whole data set to the concentrations of analytes. Partial least squares (PLS) regression is the most popular multivariate calibration method for quantitative analyses due to its ability to overcome problems common to these kinds of data, such as poor linearity, band overlap and peak interactions (Wu et al., 2008). The model fitting results can generally be evaluated according to the following chemometric indications: low root mean square error in cross-validation (RMSECV), low root mean square prediction error (RMSEP), and high calibration coefficient ($R^2$). Once the calibration model is developed, favorable predic-
tions could be expected.

In the present study, an attempt was made to estimate the pharmacokinetic parameters of clindamycin: GMO-alginate micro-
spheres versus clindamycin:alginate and plain drug after oral administra-
tion in rabbit using NIR spectroscopy. This methodology was based on the direct measurement of the transmission spectra of lyophilized plasma samples and a multivariate calibration model to determine the clindamycin concentration. The PLS calibration model was built on using the spiked plasma samples by mixing different amounts of clindamycin. The best model was used to calculate clindamycin $c_{\text{max}}$, $T_{\text{max}}$, and AUC$(0-24h)$ Values for each formulation.

2. Materials and methods

2.1. Materials

Clindamycin hydrochloride was purchased from Sigma–Aldrich Chemie GmbH (Riedstrasse, Germany). Sodium alginate was purchased from Sas chemicals (Mumbai, India). Monoolin was obtained from Danisco Emulsifiers (DIMODAN® MO 90/D, Denmark). Sorbitan monooleate (Span80) was obtained from Loba Chemie (Mumbai, India). Pluronic F127, with an average molecular weight of 12,500, was purchased from BASF (Ludwigshafen, Germany). Dichloromethane (DCM), methanol, iso-propyl alcohol, Disodium hydrogen phosphate, ethylacetate, acetonitrile (HPLC analytical grade), and calcium chloride hydrate were purchased from El-Nasr Chemicals Co. (Cairo, Egypt).

2.2. Equipments

Vortex (IKA Labortechnik, Germany), ultrasonic processor (VCX series, Sonics, USA), scanning electron microscope (SEM) (Phnom-
ProG2, Netherlands), HPLC (Shimadzu, Japan) consisted of: isocratic pump (model LC-10 AS, Shimadzu, Japan), Ultra-violet variable wavelength detector (Model SPD–10A, Shimadzu, Japan), auto-
sampler (SIL–20A, Shimadzu, Japan), centrifuge (Z236K, Hermle Labor Technik, Germany), freeze dryer (Mini Lyotrap, LTE Scientific, UK), and electronic analytical balance (XB 220A, Precesia, Swaziland) were used throughout the study. Data acquisition and data integration were done using Origin 6.0 soft-
ware.

2.3. Preparation of drug loaded Ca-alginate and GMO-alginate microspheres

Clindamycin loaded Ca-alginate microsphere were prepared by conventional water-in-oil emulsion method (Mohamed et al., 2014). Briefly, 100 mg clindamycin dissolved in 2 ml distillate water were emulsified into 10 ml of 4% (w/v) sodium alginate solution by vortexing for 2 min and further emulsified into 50 ml DCM. Microspheres were prepared by adding 8 ml of 5% (w/v) CaCl$_2$ (dissolved in 1:2 mixture of methanol and isopropyl alcohol) to the emulsion drop by drop via 10 ml syringe at 1000 rpm and stirring for 60 min to assure efficient cross-linking. Finally, microsphere suspension was allowed to stabilize on ice for about 10 min, and the microspheres were collected by filtration in vacuum, washed with isopropyl alcohol and dried at room temperature.

Using the optimum GMO:alginate ratio obtained in a previous study (Mohamed et al., 2014), microspheres containing 1:0.25 w/w alginate:clindamycin ratios were prepared by dissolving 100 mg clindamycin into 2 ml distillate water then added to the molten GM0 heated to 45 °C in a water bath. The resultant viscous cubic gel was incubated at room temperature 24 h, mixed with 1.5 ml of 2% pluronic F127 solution, then homogenized using a sonicator for 2 min at 25 °C. Drug-GMO dispersions were emulsified into 10 ml of 4% (w/v) sodium alginate solution by vortexing for 2 min, further emulsified into 50 ml DCM, and the microspheres were prepared as
described before. The prepared microspheres were examined using SEM at an accelerating voltage of 5 kV.

2.4. Animal preparation

Male albino rabbits (New Zealand) weighing 2.0–2.5 kg were selected for this study; all animals were healthy during the period of the experiment. All efforts were made to maintain the animals under controlled environmental conditions (temperature 25 °C, relative humidity 45% and 12 h alternate light and dark cycle) with 100% fresh air exchange in animal rooms. Rabbits were fed with standard diet with free access to water throughout the experiment. The animal care and handling was done according to the guidelines set by the World Health Organization, Geneva, Switzerland and the experimental protocol of animal study was performed according to the guidelines issued by ethical committee of Faculty of Pharmacy, Cairo University, Egypt. Blood samples (about 1 ml) were withdrawn from the ocular vein into heparinized tubes, centrifuged immediately at 3000 rpm for 10 min to obtain plasma samples and were stored at −20 °C for subsequent assay.

2.5. Preparation of clindamycin stock solution

An accurately weighed amount of clindamycin HCl equivalent to 10 mg of clindamycin was transferred into a 100 ml volumetric flask and diluted to volume with distilled water (100 μg/ml).

2.6. Preparation of clindamycin–plasma standard solutions

The spiked plasma samples were established by adding aliquot clindamycin dilutions to 1 ml blank plasma to get a concentration range of 0.001–10 μg/ml for calibration analysis.

2.7. Estimation of clindamycin by HPLC

The quantitative determination of drug in plasma was performed using a validated HPLC method described by Na-Bangchang et al. (2006). The separation was carried out on a reversed phase column Luna C18 (250 × 4.6 mm, 5 μm particle size) and the elution solvent consisted of a solution of 0.02 M disodium hydrogenphosphate (pH 2.8) and acetonitrile (76:24 v/v), running through the column at a flow rate of 1.0 ml/min. The chromatographic operation was carried out at 25 °C. Sample preparation (1 ml plasma) was done by a single step liquid–liquid extraction with water saturated ethylacetate (5 ml, twice extraction by mechanical tumbling). The resulting clear organic layer was separated through centrifugation at 3500 × g for 15 min, and evaporated to dryness. Samples were protected from light and stored at 4 °C until injection. For HPLC injection, samples were reconstituted with 200 μl mobile phase, and an aliquot of 100 μl was injected onto the chromatographic system. Detection was carried out at 210 nm and the quantification of the chromatogram was performed using peak area.

2.8. Estimation of clindamycin by NIR

2.8.1. Sample preparation

1.0 ml plasma (free or spiked with standard clindamycin) was measured accurately to 3 ml glass vials (17 mm diameter, and 25 mm height) containing 0.5 ml hypertonic saline (3% w/v sodium chloride) that act as salt window. All the sample vials were frozen at −50 °C for 12 h, and then arranged on freeze dryer shelves (Mini Lyotrap, LTE Scientific, UK) at 0.04 mbar vacuum, and −30 °C temperature for 12 h.

2.8.2. Data collection

The NIR spectra were collected using NIRFlex N-500 Solids Transmittance spectrophotometer (BUCHI, Switzerland) at room temperature. A single NIR spectrum was run for 3 samples from each lyophilized clindamycin–plasma concentration. Each group of 3 sample vials was placed on sample wheel, and the light transmitted through samples was measured using a sensitive external detector positioned above the sample. Each spectrum was an average of 64 scans with a wavelength increment of 0.5 nm, and the range of spectra was from 4000 cm⁻¹ to 12,500 cm⁻¹. After recording the spectra, each lyophilized sample was diluted with 1 ml distilled water then, clindamycin content was determined using the HPLC method mentioned before, and attributed to the appropriate spectra.

2.8.3. Wavelength range selection

The absorbance spectra of free clindamycin, free plasma, and plasma–clindamycin samples were compared and the NIR frequency region that involves best drug signals was selected for calibration model setting.

2.8.4. Chemometric analysis

All chemometric modeling were performed using Essential FTIR™ software (15th Edition, Operant LLC, USA). Partial least square (PLS) regression analysis was used to develop calibration models. Various pre-treatment routines; standard normal variant (SNV), multiplicative scatter correction (MSC), first and second derivatives were trialed. SNV and MSC mathematical transformation methods used mainly to remove slope variation and to correct light scatter effects, while derivation is commonly used to eliminate random fluctuations in the baseline (first derivative) and slope (second derivative) of the absorption spectra (Wu et al., 2008). The performance of the NIR model was evaluated with leave-one out cross validation (CV). This validation consists of developing a calibration model with all the samples, but one. The sample left out was then predicted by the calibration model. The calibration coefficient (R²), root mean square error of cross validation (RMSECV), and low root mean square prediction error (RMSEP) were used to select the appropriate number of PLS factors (principal components) for each model. A good model should have high calibration coefficient (R²), and low RMSECV & RMSEP values.

2.9. Drug administration and blood sampling

Rabbits were divided into 3 groups, each consisting of 6 animals. First group received conventional hard gelatine capsule containing 100 mg of free clindamycin (F1). Second and third groups received capsule containing the formulated drug/Ca-alginate (F2) and drug/GMO-alginate (F3) microspheres equivalent to 100 mg clindamycin, respectively. All capsules were administered orally as a single dose to all groups (F1–F3). The capsules were put behind the tongue to avoid their destruction due to biting. Food was withdrawn from the rabbits 12 h before drug administration and until 24 h post dosing. Blood samples (1 ml) were collected in heparinised tubes prior to the drug administration (zero time), and at 0.5, 1, 2, 3, 4, 6, 10, 14, and 24 h after dosing. All blood samples were immediately centrifuged at 3000 rpm for 10 min, and the serum was stored in a freezer at −20 °C until the time of NIR assay.

2.10. Pharmacokinetic analysis

Plasma level data obtained from the individual rabbit per each group were used to estimate the main pharmacokinetic parameters; maximum plasma concentration (Cmax, μg/ml), time required to reach maximum plasma concentration (Tmax, h), and area under the plasma concentration–time curve from time 0 to
24 h (AUC0–24, μg ml⁻¹ h) were calculated by the use of PK Solution 2.0 software package (Summit Research Services, Montrose, USA). The results were expressed as mean ± standard deviation (SD).

3. Results and discussion

3.1. Drug loaded microspheres preparation and evaluation

The alginate:clindamycin and GMO-alginate:clindamycin microspheres were prepared and the average diameters were determined from SEM images (Fig. 2). Morphological characterization showed that all microspheres were spherical in shape, about 15.7–27.4 μm in diameter and almost no polymer remnants. In a previous study, the drug entrapment efficiencies of alginate and GMO-alginate microspheres – prepared by the same method and of similar morphological characteristics – were ranged from 85.57 to 94.40%, respectively, and the GMO-alginate microspheres have successfully sustained the in-vitro release of clindamycin over 24 h time period. (Mohamed et al., 2014).

3.2. HPLC assay

Clindamycin hydrochloride HPLC chromatogram is given in Fig. 3 showing elution peak at 5.76 min. A typical calibration curve is presented in Fig. 4, which consisted of a blank-zero sample and calibration standards cover the range (0.001–10 μg/ml) prepared in rabbit plasma and chromatographed. The linearity was evaluated by calculating the linear regression correlation

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**Fig. 2.** SEM images of (a) 1:0.25 w/w alginate:clindamycin microspheres, (b) 1:0.25 w/w GMO-alginate:clindamycin microspheres, showing spherical microspheres about 15.7–27.4 μm in diameter.

**Fig. 3.** Standard HPLC chromatogram of clindamycin hydrochloride showing elution peak at minute 5.76.
3.3. NIR assay

3.3.1. Sample preparation

The preservation of plasma by means of freezing sublimation has been regarded as the most suitable method of preservation of biological substances (Ježkova 1963). This method comprises two stages: refrigeration at −20 °C or below, and drying at high vacuum for about 12 h. Fig. 5 presents lyophilization product of free plasma and plasma spiked with clindamycin.

3.3.2. Wavelength range selection

The spectrum for free clindamycin is shown in Fig. 6(a). It is clear from the figure that clindamycin exhibit characteristic signal in 8000–9200 cm⁻¹ region even in present of plasma components Fig. 6(c). This area mainly related to overtone C—H stretching (CH₃ and CH₂ groups) for clindamycin.

3.3.3. Chemometric analysis

As shown in Fig. 7, NIR spectra of clindamycin–plasma samples at concentration range 0.001–10 μg/ml show too much noise and non-linear signal response, which is not useful in constructing a calibration model. In order to improve spectral features, spectral pre-treatment was used to quantify the drug content.

The calculation of derivatives of spectral data is commonly undertaken to remove baseline shifts between spectra, while the MSC and SNV algorithms are typically employed to reduce the effects of light scattering on the spectrum. However, there are no ‘hard rules’, and the general advise in relation to development of the best NIR calibration model and method is one of trial and error, i.e., empirical trials of the benefit of such methods for the particular application. Table 1 shows the results of PLS models with different spectral pretreatments on NIR plasma samples spectra. Normalization (SNV), and second derivative smoothing gap2 pre-treatment (Fig. 8) were found useful to get the lower RMSECV and RMSEP values (0.245 and 1.164) and the nearer to (1) R² value (0.9753) (Table 1); these values reflect a good correlation compared to previous NIR chemometric analyses. (Yu and Xiang, 2008; Souza et al., 2012).

As for any multivariate regression modeling technique, model over-fitting, through use of too many PLS factors (principal components (PC)), and too wide wavelength range, is a risk in PLS model development, particularly for data sets in which the number of X variables (wavelengths) greatly exceeds the number of samples. Using 7-PC, and 8000–9200 cm⁻¹ spectral range, calibration model shows a good correlation between HPLC and NIR values (Figs. 9 and 10).
3.4. Pharmacokinetic studies

The pharmacokinetic data of F1, F2 and F3 formulations were shown in Fig.11 and Table 2. From the obtained data, it was observed that, the absorption of plain clindamycin was rapid and reached its peak plasma concentration in (0.5 h), whereas, the \( T_{\text{max}} \) for the alginate:clindamycin (F2) and GMO-alginate:clindamycin (F3) formulations were 1.0 and 4.0 h, respectively. The mean peak plasma concentrations (\( C_{\text{max}} \)) were 3.81 ± 0.8 \( \mu \text{g/ml} \) for F2 formulation, 2.37 ± 0.3 \( \mu \text{g/ml} \) for formulation F3 compared to 5.43 ± 0.7 \( \mu \text{g/ml} \) for plain clindamycin. The area under the curve over 24 h (\( \text{AUC}_{0-24} \)) is lowest for F3 and highest for the plain drug, reflecting a reduction in the bioavailability of the drug in the F2 formulation compared to the plain drug, and the F3 formulation.

Table 1

<table>
<thead>
<tr>
<th>Pre-treatment</th>
<th>( R^2 )</th>
<th>RMSECV</th>
<th>RMSEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNV</td>
<td>0.68</td>
<td>1.993</td>
<td>1.293</td>
</tr>
<tr>
<td>MSC</td>
<td>0.53</td>
<td>3.080</td>
<td>1.478</td>
</tr>
<tr>
<td>1st derivative</td>
<td>0.73</td>
<td>2.298</td>
<td>1.726</td>
</tr>
<tr>
<td>2nd derivative</td>
<td>0.91</td>
<td>1.827</td>
<td>1.412</td>
</tr>
<tr>
<td>SNV and 2nd derivative</td>
<td>0.9753</td>
<td>0.245</td>
<td>1.164</td>
</tr>
</tbody>
</table>

RMSECV: root mean square error of cross validation.
RMSEP: root mean square error of prediction.
\( R^2 \): calibration coefficient.
SNV: standard normal variant.
MSC: multiplicative scatter correction.
Fig. 8. NIR spectra of clindamycin–plasma samples after normalization (SNV), and second derivative smoothing gap2 pre-treatment.

Fig. 9. PLS principal components for clindamycin–plasma calibration model showing a minimum root mean square error of cross validation at 7 principal components.

Fig. 10. Regression plot for NIR values versus HPLC reference of clindamycin–plasma concentration.
clindamycin features, purpose, and combined pre-treatment. Although spectroscopy be used, All environment.

**Fig. 11.** Clindamycin plasma concentration–time curves following oral administration of the three formulations in rabbits; (F1) free drug, (F2) alginate:clindamycin, (F3) GMO-alginate:clindamycin.

### Table 2
Comparison of pharmacokinetic parameters of clindamycin formulations (Mean ± SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Free clindamycin (F1)</th>
<th>Alginate:clindamycin (F2)</th>
<th>GMO-alginate:clindamycin (F3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug dose (mg)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg/ml)</td>
<td>5.437 ± 0.7</td>
<td>3.812 ± 0.8</td>
<td>2.375 ± 0.3</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>0.5</td>
<td>1.0</td>
<td>4.0</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0–24&lt;/sub&gt; (µg/ml)</td>
<td>56 ± 3.7</td>
<td>55 ± 3.3</td>
<td>41 ± 2.6</td>
</tr>
</tbody>
</table>

All data significant at p < 0.01.

compared to the F2 formulation. These pharmacokinetic data could be explained by the previously reported higher drug entrapment efficiencies of GMO-alginate compared to alginate microspheres (85.57 and 94.40%, respectively) (Mohamed et al., 2014).

The increase in the T<sub>max</sub> and the decrease in the mean C<sub>max</sub> of the test formulation compared to the plain drug indicated the sustained release effect of the microsphere formulations. The higher T<sub>max</sub> and the lower C<sub>max</sub> of the F3 formulation compared to the F2 formulation reflects the positive effect of GMO on the sustained release properties of alginate microspheres.

**4. Conclusion**

In the present study, it was verified that the near-infrared spectroscopy can be used to quantify clindamycin–plasma concentration rapidly and accurately. Spectral regions and spectra pre-treatment were assayed in order to obtain the best analytical features of the PLS-NIR model. Compared to the current non-specific and time/reagent consuming methods for clindamycin plasma concentration quantification, the fast and low cost NIR combined with chemometrics could be a valuable tool for this purpose, which also does not use chemical reagents harmful to the environment. However, as NIR spectroscopy is sensitive to water and hydrogen bonding that water forms with the sample, we have used lyophilized samples to avoid any interference from water. Although the NIR spectroscopy is fast, the lyophilization process is still time consuming. Further studies should attempt to quantify clindamycin plasma concentration using liquid samples and compare its results to the results obtained in this study after excluding the bands of water; if consistent with each other, the time consuming lyophilization could be avoided.

In a previous study, a GMO-alginate microsphere was developed to provide a dosage form with improved sustained release properties compared to conventional alginate microspheres. Using NIR, the pharmacokinetics parameters of both formulations were deduced in this study. From the obtained data, it could be concluded that GMO-alginate (1:4 w/w) is a better system for once daily extended release of the water soluble clindamycin hydrochloride compared to Ca-alginate matrix alone. However, GMO-alginate microspheres have shown a possible reduced bioavailability of clindamycin compared to alginate microspheres; further evaluation of bioavailability is still needed, and the extent of reduction in bioavailability should be evaluated against the benefits of a once daily dosage form. Further studies should also assess the amount of the drug needed to provide a therapeutic plasma level of clindamycin throughout the 24h duration. Generally, these promising sustained release properties of GMO-alginate microsphere suggest that it could provide a valuable sustained release dosage form of other water soluble drugs.

**References**


