Government of India
Patent Office
Intellectual Property Office Building, Plot No. 32, Sector 14, Dwarka, New Delhi-110075
Phone- 011-28032253, 25300200
Fax: 011-28034301, 28034302
e-mail: delhi-patent@nic.in

CBR Number : 12923
Application Type: ORDINARY APPLICATION
Priority Number:
Priority Date:
Priority Country: Not Selected

To,
WADHWA JYOTI
JYOTI WADHWA H.NO. 330/10, MATA GATE, ROHTAK, HARYANA-124001, INDIA.

Received documents purporting be to an application for patent numbered 1760/DEL/2014 dated 30-06-2014 by WADHWA JYOTI of M.M. COLLEGE OF PHARMACY, M.M. UNIVERSITY, MULLANA-AMBALA, HARYANA, 133203, INDIA. relating to POLYMERIC SELF EMULSIFYING NANOCAPSULES CONTAINING CURCUMIN FOR COLONIC PHTHOLOGIES AND PREPARATION METHOD THEREOF together with the Provisional and fee(s) of ₹1760 (One Thousand Seven Hundred & Sixty only).

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(For Controller of Patents)
The purpose of the present study was to formulate polymeric self-emulsifying curcumin nanocapsules with high encapsulation efficiency, good emulsification ability, and optimal globule size for localized targeting in the colon. Formulations were prepared using modified quasiemulsion solvent diffusion method. Concentration of formulation variables, namely, $X_1$ (oil), $X_2$ (polymeric emulsifier), and $X_3$ (adsorbent), was optimized by design of experiments using Box-Behnken design, for its impact on mean globule size ($Y_1$) and encapsulation efficiency ($Y_2$) of the formulation. Polymeric nanocapsules with an average diameter of 100–180 nm and an encapsulation efficiency of 64.85 ± 0.12% were obtained. In vitro studies revealed that formulations released the drug after 5 h lag time corresponding to the time to reach the colonic region. Pronounced localized action was inferred from the plasma concentration profile ($C_{\text{max}}$ 200 ng/mL) that depicts limited systemic absorption. Roentgenography study confirms the localized presence of carrier (0–2 h in upper GIT; 2–4 h in small intestine; and 4–24 h in the lower intestine). Optimized formulations showed significantly higher cytotoxicity (IC$_{50}$ value 20.32 μM) in HT 29 colonic cancer cell line. The present study demonstrates systematic development of polymeric self-emulsifying nanocapsule formulation of curcumin for localized targeting in colon.

1. Introduction

Accumulated evidences over the years have shown that many anticancer drug molecules, such as steroids and nonsteroidal anti-inflammatory drugs, are associated with numerous side effects. Perhaps the best instance is the cardiovascular impediments imposed by the use of COX inhibitors [1, 2]. As a result, there has been an increasing demand for safer and proficient drug molecules. Curcumin, the Indian solid gold, has been reported as one of the most promising candidates of natural origin, having anticancer properties, with almost no reported side effects [3]. Therapeutic applications of curcumin (CUR), however, remain limited due to its poor absorption and rapid elimination [4]. It has been observed that more than 60–70% CUR is excreted unchanged in the faeces and the remainder is metabolized and absorbed through the intestinal mucosa and liver [5]. Numerous previously reported studies have aimed at improving poor aqueous solubility, bioavailability, alkaline stability, and/or rapid intestinal metabolism of CUR. These includes CUR-impregnated soluble dietary fibres dispersion with enhanced bioavailability (20 times) comparative free CUR [6]. CUR may also be combined with piperine, which inhibits enzymatic conjugation and allows enhanced absorption of unchanged curcuminoids into portal blood [7]. In addition, various strategies have been undertaken to deliver curcumin to intestine by multiparticulate systems [8], solid lipid nanoparticles [9, 10], and polymeric micelles [11] in cancer therapy with enhanced systemic bioavailability. However, these aforementioned systems have poor localisation efficacy due to rapid drug absorption into the systemic circulation.

A review of literature suggests that the application of carrier technology is not limited to scientific interest in
such formulations but underlines the potential and versatility in addressing the problems associated with poorly aqueous soluble drugs for localized delivery [12, 13]. New approaches, such as self-emulsifying drug delivery system, have also found their way in enhancing the solubility of CUR in colonic conditions and have several advantages over the existing ones [14, 15]. Moreover, nanocapsules (polymeric wall enveloping an oil core, confining the drug molecule within the central cavity) deliver the drug to target site in a controlled manner [16]. Novel nanocapsules bearing self-emulsification ability and high loading efficiency can effectively address the gastric resistance problem and suitably target colonic sites [17].

To the best of our knowledge, polymeric self-emulsifying nanocapsules for colon targeting have not been explored for curcumin, till date. Nanosized polymeric formulation transformed to emulsified form when it comes in contact with an alkaline medium (simulating colonic region). As a result, dissolved drug might be released in a controlled manner after initial burst release, due to dissolution of polymeric matrix of the nanoparticulate system leading to local action [18]. Present paper reports development and optimization of curcumin polymeric nanocapsule formulation, using a pH-sensitive polymer (HPMCAS-HF) possessing self-emulsifying ability and localized drug delivery in the colon.

2. Materials and Methods

2.1. Materials. Curcumin (CUR) was purchased from HiMedia, Mumbai, India. Hydroxy propyl methyl cellulose acetate succinate (HPMCAS-HF) was kindly gifted by Arihant trading Co., Mumbai, India. Capryol 90 (C-90), Lauroglycol FCC (LFCC), and Labrafac were obtained as gratis from Gattefosse Pvt. Ltd (Mumbai, India). Edible oils (isopropyl myristate, castor oil, oleic acid, ethyl oleate, corn oil, CapteX 200, apricot oil, olive oil, and soybean oil) were purchased from HiMedia, Mumbai, India. Aerosil 200 and polyvinyl alcohol (1,25,000 Mol. Wt.) were purchased from CDH, Mumbai, India. 96-well plates (A-U96) were kindly gifted by the Lipidcure Core NOF Corporation, Japan. Potassium dihydrogen phosphate was purchased from Merck, Mumbai, India. All the other chemicals and reagents used in the study were of analytical grade.

2.2. Initial Screening of Excipients

2.2.1. Solubility Studies. Solubility of CUR was determined in oils (C-90, LFCC, Labrafac, isopropyl myristate, castor oil, oleic acid, ethyl oleate, corn oil, CapteX 200, apricot oil, olive oil, and soybean oil) using saturated shake flask method as reported by Singh et al., 2010 [19]. Excess CUR was suspended in oil in a screw capped glass vial. The mixture was sonicated for 5 min to ensure uniform mixing and solubilization of CUR. The mixture was shaken at 37°C for 24 h in the shaker water bath (Accumax India Pvt. Ltd., New Delhi, India), set at 100 rpm, and allowed to stand for 48 h to attain equilibrium. After 72 h, mixtures were centrifuged at 3000 rpm for 10 min, followed by filtration through a 0.45 μm membrane filter. Analysis was carried out using a Shimadzu HPLC system (LC-2010C HT, Japan) equipped with a reverse phase Phenomenex C18 column (250 mm × 4.6 mm). Elution was carried out at room temperature (37°C), with a UV-visible detection wavelength of 425 nm. A mixture of acetonitrile: HPLC water (57: 43% v/v), pH 3.3, was used as mobile phase at a flow rate of 1.0 mL/min.

2.2.2. Experimental Design. Based on the preliminary studies, formulation excipients Capryol 90 (oil), HPMCAS-HF (polymer), and Aerosil 200 (adsorbent) were selected as the independent variables X₁, X₂, and X₃, respectively. Box- Behnken design (BBD) was applied to the optimization procedure using Design Expert (Ver. 8.0.7.1) software. A set of seventeen trial formulations (P₁–P₁₇) was prepared by varying the concentration of independent variables at three different levels (−1, 0, and +1) (Table 1). The quadratic model generated by the design has (I) as follows:

$$ Y = b₀ + b₁X₁ + b₂X₂ + b₃X₃ + b₁₂X₁X₂ + b₁₃X₁X₃ + b₂₃X₂X₃ + b₁₁X₁^2 + b₂₂X₂^2 + b₃₃X₃^2. $$

(1)

The above equation comprises the coefficient of the intercept, first-order main effect (X₁, X₂, X₃), interaction terms (X₁X₂, X₁X₃, X₂X₃), and higher order effect (X₁², X₂², X₃²), where Y is the measured response; response variables selected for the optimization purpose were mean globule size (Z-Avg) (Y₁) and encapsulation efficiency (Y₂).

2.2.3. Preparation of Curcumin Loaded Polymeric Self-Emulsifying Nanocapsules (PSN). CUR loaded PSN formulations (P₁–P₁₇) were prepared using modified quasiumulsion solvent diffusion method (Figure 1) [20, 21]. Solution of polymer (HPMCAS-HF) was prepared in ethanol: dichloromethane (1:1) mixture. CUR was incorporated in the lipidic phase of Capryol 90, followed by addition of Aerosil 200. CUR-oil mixture was emulsified with HPMCAS-HF solution using probe sonicator to yield a w/o emulsion. An aqueous polyvinyl alcohol solution (0.3% w/v) containing 0.1% sodium laurel sulfate (SLS) was prepared separately and the prepared w/o emulsion was emulsified in PVA solution, in a dropwise manner. The resulting w/o/w emulsion was stirred magnetically at 500 rpm for 4-5 h at 37°C. Dispersed droplets were solidified by diffusion of the solvent into the aqueous phase. Solidified particles were washed with distilled water thrice followed by centrifugation (25,000 g for 10 minutes at 4°C). Solidified PSN was suspended in distilled water and lyophilized at −18°C for 24 h. Resultant product was stored in a vacuum desiccator at 25°C.

2.3. Evaluation of Polymeric Self-Emulsifying Nanocapsules

2.3.1. Globule Size. The globule size of the nanocapsule formulations was determined by photon correlation spectroscopy (PCS), using Zetasizer Nano S90, Malvern, WR141XZ, UK. PSN (10 mg) were dispersed in 100 mL of phosphate buffer (pH-7.2) using vortex for 1 h and filtered through a membrane filter (0.22 μm) [15]. The filtrate was analyzed for Z-Avg and zeta potential in triplicate.
Table 1: Composition of nanocapsule formulation using Box-Behnken design.

<table>
<thead>
<tr>
<th>Independent factors</th>
<th>Coded</th>
<th>Low Actual (mg)</th>
<th>Middle Actual (mg)</th>
<th>High Actual (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>𝑋_1: conc. of Capryol 90 (oil) (mg)</td>
<td>−1</td>
<td>250</td>
<td>0</td>
<td>500</td>
</tr>
<tr>
<td>𝑋_2: conc. of HPMCAS-HF (polymeric emulsifier) (mg)</td>
<td>−1</td>
<td>100</td>
<td>0</td>
<td>150</td>
</tr>
<tr>
<td>𝑋_3: conc. of Aerosil 200 (adsorbent) (mg)</td>
<td>−1</td>
<td>75</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

Dependent variables

- 𝑌_1: mean globule size (nm)  
  *Minimize*
- 𝑌_2: encapsulation efficiency (%)  
  *Maximize*

2.3.2. Encapsulation Efficiency. CUR loaded PSN formulation theoretically equivalent to 10 mg of CUR was weighed and dissolved in 5 mL of methanol by vortex [22]. Samples were centrifuged (R-4C, Remi centrifuge, Mumbai, India) at 4000 rpm for 10 min, filtered, diluted, and quantified using HPLC. All studies were conducted in triplicate. Encapsulation efficiency was calculated as

\[
\text{Encapsulation efficiency (\%)} = \left( \frac{\text{Actual drug loaded}}{\text{Theoretical drug loaded}} \right) \times 100. \number{2}
\]

2.3.3. Emulsification Efficiency. An accurately weighed CUR loaded PSN formulation (equivalent to 10 mg of CUR) was introduced into 100 mL of simulated colonic medium (pH 7.2) [23]. Medium was agitated at 50 rpm for 2 h at 37 ± 0.5°C. Formation of emulsion was observed by visual inspection.

2.3.4. In Process Particulate Distribution. Trinocular phase contrast microscopy was used to determine the distribution of CUR during the process. A droplet of w/o/w emulsion was mounted on a slide and observed by phase contrast microscope (Metzer-M, Mathura, India).

2.3.5. Surface Morphology. The surface morphology of the optimized formulation (P5), with and without plasticizer (TEC), was examined using scanning electron microscope, SEM (EVO 18, Zeiss, Jena, Germany). The sample was fixed using double-sided adhesive tape to a brass specimen and made electrically conductive by gold coating in vacuum [24]. Samples were imaged at different resolutions (2-6 KX).

2.3.6. Differential Scanning Calorimetry. Thermal analysis of CUR, C-90, HPMCAS-HF, physical mixture of CUR with HPMCAS-HF, and optimized PSN formulation (P5) was carried out using differential scanning calorimeter (DSC-204 F1, Phoenix, NETZSCH-Geratebau GmbH, Deutschland, Germany) under nitrogen purging (50 cc/min). Samples were placed in crimped aluminium pans and were heated from ambient temperature to 250°C at 10°C/min [25].
2.3.7. X-Ray Powder Diffraction (XRPD). The diffraction pattern of CUR, HPMCAS-HF, physical mixture of CUR with HPMCAS-HF, and optimized formulation (P5) was obtained by XRPD (Bruker D8 Advance, Karlsruhe, Germany) to assess their crystallinity [26]. These were scanned over 2θ range from 10 to 35° at 0.05°/sec step size.

2.3.8. In Vitro Dissolution Studies. In vitro release of CUR from PSN formulations was determined using USP type II (Paddle type) dissolution apparatus to study the effect of pH on drug release. Formulation P1–P17 equivalent to 10 mg CUR was transferred to 325 mL of dissolution media at 37 ± 0.5°C for 2 h in simulated gastric fluid, pH 1.2; the pH of the dissolution media was then adjusted to 6.8 by the addition of 125 mL of 0.2 M trisodium orthophosphate. Dissolution was continued in phosphate buffer (pH 7.2) up to 12 h. Aliquots of 5 mL of the dissolution medium were withdrawn at predetermined time intervals and filtered through 0.45 μm nylon filter. Concentration of CUR was determined using HPLC as described previously.

In order to discriminate the formulations showing insignificant difference in release profile comparatively optimized formulation (P5), a discriminating study was carried out on formulations (P3, P5, and P10) with aforementioned dissolution conditions, but with varied paddle speed (50 and 75 rpm) and volume of dissolution media (phosphate buffer, pH 7.2), 500 and 900 mL [27].

2.3.9. Cell Viability Assay. The effect of CUR loaded PSN formulation on cell growth was determined on human colon carcinoma, HT29 cell line. The cell growth inhibitory activity of samples was evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay [11]. Cell lines were maintained in folate deficient RPMI 1640 medium under suitable conditions (supplemented with 2 mM glutamine, 1% Pen-Strep (Sigma Aldrich, St. Louis, USA), and 10% fetal bovine serum (FBS)). Cells were maintained at 37°C in a humidified atmosphere containing 5% CO2/95% relative humidity (CO2 incubator; Binder, Germany). When the cells were confluent, they were trypsinized and seeded into 96-well culture plates at a cell density of 2 × 103 cells per well and the plates were maintained under the conditions previously mentioned. Twenty-four hours later, the old medium was carefully aspirated and the cells were incubated in a logarithmic growth phase with various concentrations ranging from 0 to 30 μg/mL of free CUR, equivalent CUR loaded PSN formulation (P5), equivalent concentration of plain PSN formulation, and DMSO (control). After 24 h of incubation, the old medium was aspirated and replaced with fresh medium. MTT dye (0.5 mg/mL, 20 μL) was added to each well and the plate was incubated for further 4 h at 37°C allowing viable cells to reduce MTT into purple formazan crystal [28]. After incubation, the medium was removed and 200 μL of dimethyl sulphoxide (DMSO) was added and the optical density was measured at 450 nm using a microplate reader (Sunrise Tecan, Männedorf, Switzerland). Cell viability was expressed as a percentage compared to a control that had not been treated with either formulation or free CUR, using the following equation:

\[
\text{% Cell Viability} = \frac{N_i}{N_c} \times 100,
\]

where \(N_i\) and \(N_c\) are the numbers of surviving cells in the group treated with CUR loaded formulation and in the untreated cell group, respectively.

2.3.10. In Vivo Animal Study. In vivo study of free CUR/CUR-loaded PSN formulation was carried out on Duncan Hartley guinea pigs (250–300 g), as per the institutional protocol (MMCP/IAEC/II/23) approved by the animal ethics committee of the MM College of Pharmacy. 100 mg/kg of CUR and equivalent dose of optimized formulation (P5) were administered to guinea pigs, in groups of six animals, respectively, in fasting conditions. During the course of the studies, water was available ad libitum. Animals used for in vivo experiments were divided into three groups (\(n = 6\)). The PSN suspension (dose 100 mg/kg), suspension of pure CUR (dose 100 mg/kg), and control were administered by oral route using oral feeding needle number 18. Guinea pigs were anesthetized using chloroform and blood samples (200 μL) were withdrawn from the femoral vein in EDTA coated Eppendorf tubes at specified time intervals (0, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 h). Blood samples were immediately centrifuged for 5 min and plasma was separated. A Shimadzu LC-2010C HPLC system equipped with a UV-visible detector was used to quantitatively determine the concentration of CUR and 4-hydroxybenzophene (internal standard, IS) in plasma samples. 100 μL of plasma was mixed with 50 μL of IS working solution (8 μg/mL) in an Eppendorf tube. The plasma was then extracted twice with 250 μL of acetonitrile by vigorous mixing for 5 min and was centrifuged at 3000 g for 15 min. 20 μL of the supernatant was injected directly into the column and was analysed quantitatively. Elution was carried out at 300 and 425 nm for 4-hydroxybenzophene and CUR, respectively [29].

3. Results

CUR showed a limited aqueous solubility (0.6 μg/mL), whereas it had significantly higher solubility in oils (Figure 2). CUR showed highest solubility (11.41 ± 0.23 mg/g) in C-90 and thereby selected as the oil phase (independent variable \(X_1\)) for PSN formulation. On the basis of solubility of polymer in organic solvents (ethanol, acetone, isopropyl alcohol, and dichloromethane), ethanol and dichloromethane (1:1) were selected as the organic phase.

3.1. Optimization of Formulation Using Design of Experiments. Box- Behnken design (BBD) of experiments was applied to the present study to investigate the effect of independent variables \(X_1, X_2, \) and \(X_3\) (oil, polymer, and adsorbent) concentration, respectively, on dependent variables \(Y_1\) and \(Y_2\) (globule size and encapsulation efficiency, resp.) [30]. Analysis of variance (ANOVA) was applied to determine
Table 2: Combination levels of independent variables and the outcomes of response variables by Box-Behnken design.

<table>
<thead>
<tr>
<th>Batch number</th>
<th>Independent factors</th>
<th>Actual value</th>
<th>Predicted value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Capryol 90</td>
<td>HPMCAS-HF</td>
<td>Aerosil 200</td>
</tr>
<tr>
<td>P1</td>
<td>−1</td>
<td>−1</td>
<td>0</td>
</tr>
<tr>
<td>P2</td>
<td>+1</td>
<td>−1</td>
<td>0</td>
</tr>
<tr>
<td>P3</td>
<td>−1</td>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td>P4</td>
<td>+1</td>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td>P5</td>
<td>−1</td>
<td>0</td>
<td>−1</td>
</tr>
<tr>
<td>P6</td>
<td>+1</td>
<td>0</td>
<td>−1</td>
</tr>
<tr>
<td>P7</td>
<td>−1</td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td>P8</td>
<td>+1</td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td>P9</td>
<td>0</td>
<td>−1</td>
<td>−1</td>
</tr>
<tr>
<td>P10</td>
<td>0</td>
<td>+1</td>
<td>−1</td>
</tr>
<tr>
<td>P11</td>
<td>0</td>
<td>−1</td>
<td>+1</td>
</tr>
<tr>
<td>P12</td>
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<td>+1</td>
<td>+1</td>
</tr>
<tr>
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<td>0</td>
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</tr>
<tr>
<td>P16</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P17</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Standard deviation of the observed responses was within ±5% (n = 3).

The model proposes (4) for globule size

\[ Y_1 = 176.31 + 12.95X_1 - 8.39X_2 + 8.01X_3 - 9.343X_1^2 + 3.34X_2^2 - 8.20X_3^2 + 2.64X_1X_2 \]  

\[ - 13.49X_1X_3 - 6.65X_2X_3 \]  

(\(F\) value = 6.531, \(R^2 = 0.8935\), and adequate precision = 11.009.)

Globule size was highest in batch P2 at higher levels of oil, low level of polymer, and mid level of adsorbent and was lowest in batch P5 at low levels of oil and adsorbent and mid level of polymer (Figure 3(a)). Response \(Y_1\) was significantly influenced by \(X_1\), \(X_2\), \(X_3\), and \(X_1X_3\) (Supplementary Table 1 available online at http://dx.doi.org/10.1155/2014/516069).

3.2.2. Encapsulation Efficiency. Regression analysis for response \(Y_2\) (encapsulation efficiency) suggested quadratic model and the cubic model was aliased due to insufficient design points to estimate the coefficients (Table 3). ANOVA data suggested regression to be significant (\(P < 0.01\)).

The model proposes polynomial equation (5) for percentage drug encapsulation as follows:

\[ Y_2 = 71.31 + 6.01X_1 - 11.67X_2 + 4.37X_3 + 5.71X_1^2 \]

\[ - 6.91X_2^2 - 17.44X_3^2 - 6.85X_1X_2 + 6.88X_1X_3 \]

\[ - 5.71X_2X_3 \]  

(\(F\) value = 10.38, \(R^2 = 0.9303\), and adequate precision = 14.47.)

Synergistic effects of \(X_1, X_2, X_3, X_1^2\), and \(X_2^2\) and antagonistic effects of \(X_2, X_3, X_1X_2, X_2X_3, X_1^2\), and \(X_3^2\) on \(Y_2\) were
Table 3: Regression analysis for mean globule size and encapsulation efficiency.

<table>
<thead>
<tr>
<th>Response</th>
<th>Model</th>
<th>Std. dev.</th>
<th>$R^2$</th>
<th>Adjusted $R^2$</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean globule size (nm)</td>
<td>Linear</td>
<td>12.79</td>
<td>0.532</td>
<td>0.424</td>
<td>Suggested</td>
</tr>
<tr>
<td></td>
<td>Second order</td>
<td>10.93</td>
<td>0.737</td>
<td>0.579</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Quadratic</td>
<td>8.31</td>
<td>0.893</td>
<td>0.756</td>
<td>Suggested</td>
</tr>
<tr>
<td></td>
<td>Cube</td>
<td>6.26</td>
<td>0.965</td>
<td>0.862</td>
<td>Aliased</td>
</tr>
<tr>
<td>Encapsulation efficiency (%)</td>
<td>Linear</td>
<td>13.60</td>
<td>0.389</td>
<td>0.248</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Second order</td>
<td>13.77</td>
<td>0.518</td>
<td>0.229</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Quadratic</td>
<td>6.26</td>
<td>0.930</td>
<td>0.840</td>
<td>Suggested</td>
</tr>
<tr>
<td></td>
<td>Cube</td>
<td>2.15</td>
<td>0.995</td>
<td>0.981</td>
<td>Aliased</td>
</tr>
</tbody>
</table>

Figure 3: Cube surface graphs for the responses of Capryol 90, HPMCAS-HF, and Aerosil 200. (a) Mean globule size; (b) % encapsulation efficiency.

observed. Encapsulation efficiency was highest in batch P2 at higher levels of oil, low level of polymer, and mid level of adsorbent and was lowest in the batch P12 at mid level of oil and high level of polymer and adsorbent (Figure 3(b)). Significance of results has been confirmed by observed $P$ value ($<0.03$) for each factor (Supplementary Table 1).

3.2.3. Identification and Evaluation of Optimum Formulation Using the Desirability Function. PSN formulation with a composition consisting of 250 mg C-90 (oil), 150 mg HPMCAS-HF (polymer), and 75 mg A-200 (adsorbent) was observed to be optimal, in terms of desired mean globule size and encapsulation efficiency (Figure 4(a)). Figure 4(b) shows the highest desirability factor 1.00 and the overlay plots in a varied range of oil and polymer for optimized formulation.

3.2.4. In Process Particulate Distribution. Figure 5 shows that the drug particles were uniformly distributed within the nanocapsule. The shell of the particles appears as dark, while the inner core appears as yellowish green.

3.2.5. In Vitro Dissolution Studies. Figure 6(a) illustrates the drug release profile of CUR from PSN formulations (P1–P17). Arround 6% of drug release was observed in 0.1N HCl (pH 1.2), whereas less than 20% of drug was released in simulated intestinal fluid (pH 6.8). However, insignificant discrimination was observed in selected dissolution test conditions (simulated colonic fluid (pH 7.2).

By increasing the dissolution medium volume (phosphate buffer, pH 7.2) up to 900 mL, the percentage of drug release observed is more than 60% when compared to 500 mL of the same medium at both paddle speeds (50 and 75 rpm). Dissolution profiles of formulations (P3, P5, and P10) in 900 mL of phosphate buffer (pH 7.2) and 50 rpm paddle speed are shown in Figure 6(b). Percentage drug release of three formulations (P5, P3, and P10) in simulated phosphate buffer (pH 7.2; 900 mL) was observed at 72.19±2.13, 65.8±1.58, and 60.27±1.72%, respectively, whereas 58.15±1.86, 56.07±1.12, and 53.99±0.92% of drug release were observed in simulated phosphate buffer (pH 7.2; 500 mL) from three formulations (P5, P3, and P10) respectively.

3.2.6. Differential Scanning Calorimetry (DSC). DSC thermograms of CUR, HPMCAS-HF, C-90, physical mixture of CUR with HPMCAS-HF, and the optimized formulation (P5) are shown in Figure 7. A sharp endothermic melting peak of CUR appeared at 180.71°C indicating its crystalline nature. HPMCAS-HF and C-90 did not show any peak over the entire
range of temperature. Optimized formulation (P5) did not show any melting endothermic peak owing to its amorphous nature.

3.2.7. X-Ray Powder Diffraction (XRPD). XRPD of CUR describes its crystalline nature. Majority of peaks for CUR occurred at 16.97, 25.20, 16.92, 24.19, 27.02, 25.15, 24.24, 26.97, 17.02, 27.07, 25.30, 23.03, 24.14, 26.92, 22.98, and 28.59° 2θ, whereas peak with highest intensity was observed at 25.25 (Figure 8).

3.2.8. Scanning Electron Microscopy (SEM). The surface morphology of the optimized formulation (P5) obtained from SEM images is shown in Figure 9. SEM of optimized formulation (P5) with plasticizer appeared with smooth surface, whereas significant pores with rough surface can be seen in images captured for optimized formulation.

3.2.9. Cell Viability Assay. Viability of cells was measured using the MTT test to evaluate the cytotoxicity of CUR on HT29 cell lines. Results of cell viability assay are shown in Figure 10. The IC50 value of the optimized PSN formulation (P5) was found to be 20.32 micro molar, while that of free CUR had 28.56 micro molar. Compared to DMSO treated cells, no cytotoxicity was observed in the cells exposed to blank PSN formulation. Insignificant change was observed after performing the test in similar manner up to 72 h.

3.2.10. In Vivo Animal Study. Plasma concentration time profile of optimized formulation and plain CUR are represented in Figure 11. Pharmacokinetic profile of optimized formulation was evaluated, compared to pure CUR. Concentration of CUR was detectable up to 24 h although insignificant concentration of drug (Cmax 200 ng/mL) was observed which may be due to the slow clearance rate leading to greater enhancement in elimination half-life and correlates well with in vitro release data.

The results are supported with roentgenographic images (Figure 12) of guinea pig at different time points. Images indicated the presence of contrast which represents the distribution of formulation in GIT at various time points such as from 0 to 2 h in upper GIT, from 2 to 4 h in the small intestine, and from 4 to 24 h in the lower intestinal region (up to anus), whereas plain CUR showed marked availability in lower GIT after 6 h which represents the elimination of the drug.

4. Discussion

Polymeric nanocapsules of curcumin were prepared by modified quasiemulsion solvent diffusion method, using an enteric polymer (HPMCAS-HF), which could obviate the issues
related to use of high concentration of surfactant (30–70%) in conventional self-emulsifying formulations.

Formation of a fine emulsion is an important parameter to prevent precipitation and recrystallization of the drug from formulation. The rate of emulsification depends on the ratio of polymer and adsorbent and the concentration of oil used in the formulation. The high viscosity of HPMCAS-HF may contribute to the rate of emulsification. Similarly, higher oil concentration increased the interfacial fluidity and accelerates the progress of emulsification [31].

Physiochemical properties, namely, surface morphology, globule size, encapsulation efficiency, and polymorphic change, of nanocapsule formulation should impact drug’s release pattern. Release rate is strongly influenced by the surface morphology of drug-loaded nanocapsules. The formulation was observed to exhibit gastric resistance during the first 5 h and thereafter exhibited a controlled release pattern up to 12 h. The controlled release profile might be attributed to smooth surface and delivery mechanism of polymeric nanocapsules probably by surface erosion. It has been observed that higher concentration of polymer extends the duration, due to the formation of crystalline gel at the oil-water interface. This relationship agrees well with the results of Trotta, 1999, who proposed transformation from one liquid crystalline structure to another during the emulsification process [32]. After 5 h lag time, enteric polymer dissolved when the pH was changed to 7.2, corresponding to the pH of the colon. Therefore, considering the GI transit time from stomach to colon of 4 to 6 h, present formulation could serve as potential carriers for delivery of curcumin to colon [33].

The concentration of polymer (HPMCAS-HF) and adsorbent (A-200) was also found to control the rate of drug release. As shown in Figure 6, increasing the amount of polymer as well as the adsorbent resulted in a considerable decrease in drug release. However, insignificant discrimination was observed in selected dissolution test conditions. It may be due to maintenance of nonsink conditions (poor
solubility in dissolution media). To establish dissolution test conditions for release characteristics of different formulations, discriminatory study was included. Data observed from discriminatory study showed a significant difference in % cumulative drug release between selected formulations (P3, P5, and P10) with increased volume of dissolution medium (900 mL), whereas the slowest paddle speed (50 rpm) results in steeper drug release profile, typically leading to a higher
discriminating efficiency. It may be due to increase in the solubility of drug in enhanced dissolution media (maintenance of sink conditions).

DSC thermograms indicated a change in the physical state of the drug from the crystalline to the amorphous state in PSN formulation. Amorphous state of CUR was further confirmed by the presence of a halo pattern in PXRD, a characteristic of the amorphous form [34]. Appearance of halo pattern (PXRD spectrum) and absence of melting endotherm (DSC thermogram) show that the drug is dispersed in a polymer matrix at a molecular level and stabilized in its amorphous form of polymer [35].

Literature suggests that systems less than 200 μm may be efficiently engulfed by the macrophages present in the colon tissue, thus exhibiting effective localized delivery [36]. Therefore, a polymer formulation with globule size less than 200 μm was chosen for the optimal formulation. Response surface analysis as design of experimental approach was used to identify the effect of variables on globule size and percentage encapsulation efficiency. It has been observed that the mean globule size increased with increase in oil concentration (Capryol 90) and the adsorbent, whereas it decreased with increasing the polymer concentration (HPMCAS-HF). Standardized effects of the Capryol 90 (oil), HPMCAS-HF (polymer), and Aerosil 200 (adsorbent) and their interaction on mean globule size ($Y_j$) are described in Supplementary Figure 1A.

Drug encapsulation efficiency was found to be affected by the concentration of emulsifier (HPMCAS-HF) as well as the stabilizer (PVA). Formulation with high HPMCAS-HF and PVA concentration showed poor encapsulation efficiency, probably due to an increased formulation viscosity [37]. Furthermore, encapsulation efficiency, increased with increase in oil concentration, however, decreased with increase in concentration of polymer and adsorbent (Supplementary Figure 1B). Design suggested formulation (P5) with all desirable parameters as optimized formulation. Selection was based upon the levels of factors that yielded maximum encapsulation efficiency, optimal globule size, and controlled drug release.

In optimized formulation, localized delivery of CUR was investigated by in vivo study in the guinea pig model. Results obtained from plasma drug concentration time profile represent an insignificant amount of drug in plasma ($C_{max} = 200$ ng/mL), suggesting limited systemic uptake of the formulation.

Cytotoxicity assay on drug loaded nanocapsules was conducted on HT29 cell lines to estimate the cell viability with free CUR, blank nanocapsules, and control (DMSO). Results demonstrated that CUR loaded PSN formulation significantly inhibited the growth of the cell lines; however, viability was less than free CUR and DMSO. Blank nanocapsules were treated with cell lines (HT-29) to verify whether a decrease in % viability was due to polymeric nanocapsule or not. It was observed that blank polymeric nanocapsules did not affect the cellular viability of HT-29 cells as compared to PSN formulations. This suggests that PSN formulations release the drug in controlled fashion in the vicinity of proliferating cell lines comparatively blank nanocapsules.

Roentgenographic study was performed on animal model (guinea pig) as this model is analogous to human physiology, also having same transit time (GI to colon) 4–6 h as that of humans. The study has been performed to evaluate the kinetics of PSN formulation in GI. Images indicate that the PSN formulation safely reached colon, which is also presented by formulations, in vitro, with sufficient gastric resistance and lag time. The evaluation of the results obtained at different stages (time points) suggests that PSN formulation is present starting from initial time point (i.e., 30 min) till 24th h. It can be observed that the formulation reaches intestinal region

Figure 12: Roentgenography study in guinea pigs. (a) Plain CUR. (b) CUR loaded optimized formulation (PSN) (P5) (where I: blank, II: after 30 min administration of formulation, III: after 1 h administration of formulation, IV: after 2 h administration of formulation, V: after 4 h administration of formulation, VI: after 6 h administration of formulation, VII: after 12 h administration of formulation, and VII: after 24 h administration of formulation).
after 4 h (Figure 12(b) (V)), whereas, in case of CUR, there is no such indication. Further, Figure 12(b) (VIII) represents PSN formulation in lower intestine up to 24 h.

Results favour the conditions, such as limited systemic absorption (plasma drug profile), intact drug until reaching the large intestine (roentgenographic study), and effective delivery of drug to target site (cell line study), required for localized delivery [36]. Therefore, it can be concluded that the developed formulation could be considered as a promising delivery strategy towards localized targeting of CUR to colonic region for the effective treatment of colorectal pathologies.

5. Conclusion

In the present study, a polymeric self-emulsifying nanocapsule formulation of curcumin was successfully developed. Optimization of oil, polymeric emulsifier, and surfactant was undertaken by Box-Behnken design, finally generating an optimal formula for nanocapsule formulation. Capryol 90 (oil phase), 250 mg, HPMCAS-HF (polymeric emulsifier), 250 mg, and Aerosil 200 (adsorbent), 75 mg, were opted for optimized formulation. Optimized formulation follows the conditions required to deliver a drug in the colon locally. Roentgenographic studies are in close agreement with in vitro dissolution studies. The present work paved way to coin a methodology for the systematic development of polymeric self-emulsifying nanocapsule for localized delivery in colonic region.

Abbreviations

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<tr>
<th>Acronym</th>
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<tr>
<td>CUR</td>
<td>Curcumin</td>
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<td>PSN</td>
<td>Polymeric self-emulsifying nanocapsules</td>
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<tr>
<td>XRPD</td>
<td>X-ray powder diffraction</td>
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<tr>
<td>HPMCAS-HF</td>
<td>Hydroxy propyl methyl cellulose acetate succinate-HF</td>
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<tr>
<td>SGF</td>
<td>Simulated gastric fluid</td>
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<tr>
<td>SIF</td>
<td>Simulated intestinal fluid</td>
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<tr>
<td>FbD</td>
<td>Formulation by design</td>
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<td>CAS</td>
<td>Chemical abstract service</td>
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<td>LFCC</td>
<td>Lauroglycol FCC</td>
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<td>C-90</td>
<td>Capryol 90</td>
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<td>RSM</td>
<td>Response surface methodology</td>
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<td>BBD</td>
<td>Box-Behnken design</td>
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<td>A-200</td>
<td>Aerosil 200</td>
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<td>DS</td>
<td>Design space</td>
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<tr>
<td>QbD</td>
<td>Quality by design</td>
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<tr>
<td>HPLC</td>
<td>High performance liquid chromatography</td>
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<tr>
<td>PCS</td>
<td>Photon correlation spectroscopy</td>
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<td>SEM</td>
<td>Scanning electron microscope</td>
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<td>TEM</td>
<td>Transmission electron microscope</td>
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<tr>
<td>PVA</td>
<td>Polyvinyl alcohol</td>
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<tr>
<td>GIT</td>
<td>Gastrointestinal tract</td>
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<tr>
<td>ICH</td>
<td>International conference on harmonization</td>
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<td>COX</td>
<td>Cyclooxygenase</td>
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Conflict of Interests

The authors report no conflict of interests.

Acknowledgments

The authors are thankful to Banasthali University, Rajasthan, India, and MM Medical College & Hospital for providing facilities for research work and roentgenographic study, respectively. Thanks are also due to Department of Physics, Rajasthan University, Rajasthan, for SEM facility and Mr. Anurag Tyagi (Gattefosse, Mumbai, India) for gifting lipid samples (Capryol 90 (C-90), Lauroglycol FCC (LFCC), and Labrafac).

References


Potential of Plant Mucilages in Pharmaceuticals and Therapy

Jyoti Wadhwa¹*, Anroop Nair² and Rachna Kumria³

¹Banasthali Vidyapith, Banasthali, Jaipur, India; ²Department of Pharmaceutical Sciences, College of Clinical Pharmacy, King Faisal University, Al-Ahsa, KSA; ³MMCP, M.M. University, Mullana (Ambala), Haryana, India

Abstract: Mucilages, and in particular plant mucilages, have gained more attention over the last few decades due to their reputable medicinal properties. Some publications have appeared in reputable Scientific Journals that have made appreciable contributions to the discovery of the functions and utilizations of such naturally occurring products. Therapeutic value of mucilages has been extended to wound healing, diabetes, immunostimulation, cancer, angiotensin converting enzyme inhibition, stomachic, and antioxidant properties. Based on their sustaining capacities as well as binding and gelling properties, mucilages have been proposed to be one of the most useful materials to modulate drug delivery. Chemical analysis reveals that generally these contain monosaccharides along with a range of other organic and inorganic components. Although physiological properties of various plant mucilages have been described, it still remains uncertain as to which of the component(s) is responsible for these physiological properties. Further research needs to be done to unravel the myth surrounding the biological activities and the functional properties of them. This review presents an overview of the current status and knowledge on the applications of plant mucilages as therapeutic agent and pharmaceutical additives.

Keywords: Drug delivery, Mucilages, Pharmaceutical Additive.

INTRODUCTION

Natural materials from plant origin have been used since ancient times by animals and humans for their common ailments. Different parts of plant species have been used to treat inflammation, diarrhoea, stomachache, cough, topical infections etc. [1-3]. Similarly, animals living in the wild are known to consume these natural healers to treat different diseases and disorders [4]. With time, more and more information about the application of plant species in medical field has been revealed and an extensive human effort has been initiated to create a scientific database about the application of these plant species in human health and diseases.

Newer technological advances lead to the isolation of numerous active molecules from plant species for the treatment of various diseases [5]. Taking lead from natural molecules, the synthetic chemists have attempted to produce vast number of synthetic compounds with desirable attributes. However, the use of natural mucilages still remains attractive because of their intrinsic advantages such as non-toxic nature, inexpensive, biodegradable and biocompatible behaviour, as well as their easy availability in nature. Alternatively, attempts were also made to modify natural materials to obtain tailor-made materials with desirable attributes.

Apart from the medicinal use, plant materials have been found to exhibit several other applications in pharmaceutical, cosmetic, textile, paint and paper industries [6]. Several plant materials have been screened for their use as a pharmaceutical additive. Among these, mucilage and gums are most widely studied as a pharmaceutical additive.

Typically, mucilages are naturally occurring highly branched hydrophilic polysaccharides (with molecular weight > 2,000,000) of varying detailed structure [7]. Chemically, mucilages are similar to gums and pectin but differ in certain physical properties. For instance, gums swell in water to form sticky colloidal dispersions, whereas mucilages form slippery, aqueous colloidal dispersions [8]. Gums are tacky, while the mucilages are slimy. Various properties of gums and mucilages are summarized in Fig. (1). Mucilages are also the normal metabolic product of plants whereas gums are the pathological products. These mucilages are produced in the epidermal cells of the seed coat, the transmitting tract of the pistil, and the outer layer of the root cap of several plant families (Brassicaceae, Solanaceae, Linaceae, and Plantaginaceae) [9]. Mucilages retain water and have an active role in germination process.

As an active ingredient, plant mucilages have demulcent property and are used as a cough suppressant. They are also known for their laxative property. Applications of mucilage have further been extended in the pharmaceutical industries, for their use as thickeners, water retention agents, suspending agents and disintegrants [10]. Key applications of plant mucilages in pharmaceuticals and therapy are represented in Fig. (2). Indeed, mucilages possess excellent excipient characteristics such as non toxicity, good biocompatibility, control drug release etc.

Although, mucilages exhibits several required excipients properties, they are yet to be completely explored. As the demand for the natural materials are increasing, the pharmaceutical researchers in this field are still tapping the newer plant sources to discover novel plant derived excipients to replace the synthetic products [11]. However, there are several challenges which limit the identification and isolation of mucilages with higher yield and consequently the applica-
EMULSION FORMING DRUG DELIVERY SYSTEM FOR LIPOPHILIC DRUGS

JYOTI WADHWA*, ANROOP NAIR and RACHNA KUMRIA

M.M. College of Pharmacy, M.M. University, Mullana (Ambala), Haryana, India

Abstract: In the recent years, there is a growing interest in the lipid-based formulations for delivery of lipophilic drugs. Due to their potential as therapeutic agents, preferably these lipid soluble drugs are incorporated into inert lipid carriers such as oils, surfactant dispersions, emulsions, liposomes etc. Among them, emulsion forming drug delivery systems appear to be a unique and industrially feasible approach to overcome the problem of low oral bioavailability associated with the BCS class II drugs. Self-emulsifying formulations are ideally isotropic mixtures of oils, surfactants and co-solvents that emulsify to form fine oil in water emulsions when introduced in aqueous media. Fine oil droplets would pass rapidly from stomach and promote wide distribution of drug throughout the GI tract, thereby overcome the slow dissolution step typically observed with solid dosage forms. Recent advances in drug carrier technologies have promulgated the development of novel drug carriers such as control release self-emulsifying pellets, microspheres, tablets, capsules etc. that have boosted the use of “self-emulsification” in drug delivery. This article reviews the different types of formulations and excipients used in emulsion forming drug delivery system to enhance the bioavailability of lipophilic drugs.

Keywords: lipid based formulations, emulsion forming drug delivery system, self-emulsification

The advances in combinatorial chemistry has lead to tremendous increase in the number of poorly water soluble drugs, and currently, more than 40% of new pharmacologically active chemical entities are lipophilic and exhibit poor aqueous solubility. However, the oral delivery of lipophilic drugs presents a significant challenge to pharmaceutical scientists due to their inherent low aqueous solubility, which generally leads to poor oral bioavailability, high intra- and inter-subject variability and lack of dose proportionality (1). Many formulation approaches are presently being employed to tackle the formulation challenges of biopharmaceutical class II (BCS) drugs, either by pre-dissolving the compound in a suitable solvent and subsequently filling the formulation into capsules (2) or by formulating as solid solution using water-soluble polymers (3). Nevertheless, these approaches can probably resolve the issue related to initial dissolution of drug molecules in aqueous environment within the GI tract to certain extent. However, major limitations like drug precipitation during dispersion of formulation in the GI tract or drug crystallization in the polymer matrix remain unresolved. Therefore, in case of such formulations, the assessment of physical stability using techniques such as differential scanning calorimetry or X-ray crystallography is necessary.

Various formulation approaches including carrier technology offer an intelligent approach for enhancing the solubility of poorly soluble drug molecules. Improvement in oral bioavailability of these molecules utilizing lipid based formulations has received much attention in the recent past. Lipids are perhaps one of the most versatile excipient classes currently available, provide the formulator a great potential option for improving and controlling the absorption of lipophilic drugs, where typical formulation approaches failed, or when the drug itself is oil (i.e., Dronabinol, ethyl icosapentate). Moreover, with such formulations, there is lower potential for precipitation of lipophilic drug molecules during dilution in the GI tract, as partitioning kinetics will favor the drug to be remained in the lipid droplets (4).

A review on the literature denotes that the application of carrier technology is not limited to the scientific interest in oral lipid-based formulations but reinforces the promise and versatility in addressing the issues related to oral delivery of several poorly soluble drug molecules. New approaches, such as self-emulsification systems, have also found

* Corresponding author: e-mail: jyotiwadhwa29@gmail.com; phone no.: 091-08059930171
Self-emulsifying therapeutic system: a potential approach for delivery of lipophilic drugs

Jyoti Wadhwa*, Anroop Nair, Rachna Kumria

M.M. College of Pharmacy, M.M. University, Mullana, Ambala, Haryana, India

Self-emulsifying therapeutic system (SETs) provide an effective and intelligent solution to the various issues related to the formulation of hydrophobic drugs with limited solubility in gastrointestinal fluid. Although the potential utility of SETs is well known, only in recent years has a mechanistic understanding of the impact of these systems on drug disposition emerged. These in situ emulsion-forming systems have a high stability when incorporated in various dosage forms. SETs are being looked upon as systems which can overcome the problems associated with delivery of poorly water soluble drugs. An in-depth knowledge about lipids and surfactants that can contribute to these systems, criterion for their selection and the proportion in which they can be used, represent some crucial factors determining the in vivo performance of these systems. This article presents a comprehensive account of various types of self-emulsifying formulations with emphasis on their composition and examples of currently marketed preparations.

**Uniterms:** Lipid based formulations. Self-emulsifying therapeutic system. Self-emulsification.

O sistema terapêutico auto-emulsionante (SETs) fornece solução eficaz e inteligente para os vários problemas relativos à formação de farmacêuticos hidrofóbicos com solubilidade limitada no fluido gastrointestinal. Embora a utilidade potencial dos SETs seja bem conhecida, no recentemente se compreendem, mecanisticamente, o impacto desses sistemas na disposição de farmacêuticos. Estes sistemas de formação de emulsão in situ têm alta estabilidade, quando incorporados em várias formas de dosagem. Os SETs têm sido considerados como sistemas que podem resolver problemas associados à liberação de fármacos pouco solúveis em água. O conhecimento profundo dos lipídios e tensioativos que podem ser utilizados para esses sistemas e o critério para a sua seleção e proporção na qual eles são utilizados são alguns dos fatores cruciais que determinam o desempenho do sistema in vivo. Este artigo apresenta uma relação abrangente de vários tipos de formulações auto-emulsionantes, com ênfase em sua composição e exemplos das preparações que são correntemente comercializadas.

**Uniterms:** Formulações baseadas em lipídios. Sistema terapêutico auto-emulsionante. Auto-emulsificação.

INTRODUCTION

In the last decade, one of the major evolutions in the areas of pharmacuetics and drug delivery was the recognition of benefits of formulating low water soluble actives as lipid based formulations, a process frequently referred to as a self-emulsifying therapeutic system. Low aqueous soluble compounds include a significant and increasing proportion of drug candidates, often viewed as high-risk drug candidates (Chong-Kook, Park, 2004; Gilyar et al., 2006; Fahr and Liu, 2007; Stegemann et al., 2007).

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*Correspondence: Jyoti Wadhwa, M. M. College of Pharmacy, M. M. University, Mullana, Ambala, Haryana - India. E-mail: jyotiwadhwa29@gmail.com

Krishnaiah, 2010). The challenge lies in formulating these poorly-water soluble drug candidates. Extensive research is being carried out by formulation/drug delivery scientists to develop strategies to augment the solubility and delivery of biopharmaceutical classification system (BCS) class II and IV molecules (Benet et al., 2008; Dressman et al., 2001). Some approaches exploited to enhance drug solubility include preparation of solid dispersions (Sethia, Squillante, 2003; Leuner, Dressman, 2004), formulation of soft gelatin capsules (Gullapalli, 2010), cyclodextrin inclusion complexes (Stella, Quaren, 2008; Davis, Brewster, 2004), melt extrusion (Breitenbach, 2002), emulsions (Bittner, Mountfield, 2002), micro-emulsions.
Enhanced oral bioavailability of acyclovir by inclusion complex using hydroxypropyl-\(\beta\)-cyclodextrin

Anroop B. Nair\(^1\), Mahesh Attimarad\(^1\), Bandar E. Al-Dhubiab\(^1\), Jyoti Wadhwa\(^2\), Sree Harsha\(^1\), and Mueen Ahmed\(^1\)

\(^1\)Department of Pharmaceutical Sciences, College of Clinical Pharmacy, King Faisal University, Al-Ahsa, Kingdom of Saudi Arabia and
\(^2\)M.M. College of Pharmacy, MM University, Mullana, Ambala, India

Abstract

The therapeutic potential of acyclovir is limited by the low oral bioavailability owing to its limited aqueous solubility and low permeability. The present study was a systematic investigation on the development and evaluation of inclusion complex using hydroxypropyl-\(\beta\)-cyclodextrin for the enhancement of oral bioavailability of acyclovir. The inclusion complex of acyclovir was prepared by kneading method using drug: hydroxypropyl-\(\beta\)-cyclodextrin (1:1 mole). The prepared inclusion complex was characterized by Fourier transform infrared spectroscopy, differential scanning calorimetry, NMR spectroscopy and evaluated in vitro by dissolution studies. In vivo bioavailability of acyclovir was compared for inclusion complex and physical mixture in rat model. Phase solubility studies indicate the formation of acyclovir-hydroxypropyl-\(\beta\)-cyclodextrin complex with higher stability constant and linear enhancement in drug solubility with increase in hydroxypropyl-\(\beta\)-cyclodextrin concentration. Characterization of the prepared formulation confirms the formation of acyclovir-hydroxypropyl-\(\beta\)-cyclodextrin inclusion complex. Dissolution profile of inclusion complex demonstrated rapid and complete release of acyclovir in 30 min with greater dissolution efficiency (90.05 \(\pm\) 2.94\%). In vivo pharmacokinetic data signify increased rate and extent of acyclovir absorption (relative bioavailability \(\sim\)1.60\%; \(p<0.0001\)) from inclusion complex, compared to physical mixture. Given the promising results in the in vivo studies, it can be concluded that the inclusion complex of acyclovir could be an effective and promising approach for successful oral therapy of acyclovir in the treatment of herpes viruses.

Introduction

Acyclovir is a well-known antiviral agent used for the treatment of herpes viruses such as herpes simplex virus type I/II and varicella zoster (Spruance & Kriessel, 2002; Lin et al., 2003). Existing treatment modalities using acyclovir for herpes infections include oral, parenteral and topical therapy (Cortesi & Esposito, 2008). However, topical therapy is considered to be less effective due to the low skin permeability of acyclovir into the target site (Spruance et al., 2002). On the other hand, oral drug delivery is the most appropriate and patient compliant method as it offers several advantages and was preferred over other routes. Following oral therapy, the absorption of acyclovir was found to be slow, variable and incomplete with low oral bioavailability (15–30\%) (Laskin, 1983; Fletcher & Bean, 1985; Arnal et al., 2008). Therefore the oral therapy of this drug required frequent administration of high dose of acyclovir, which leads to potential systemic adverse effects such as acute renal failure and neurotoxicity (Johnson et al., 1994). There has been intensive effort to improve the bioavailability of acyclovir following oral delivery. Several approaches have been attempted to develop effective drug delivery system for the successful delivery of acyclovir (Cortesi & Esposito, 2008). In one approach, vesicular carrier systems such as liposomes, niosomes, microparticles and nanoparticles were developed (Jain et al., 2005; Attia et al., 2007; Mukherjee et al., 2007; Calderón et al., 2013). On the other hand, drug discovery groups have synthesized prodrugs of acyclovir to improve the therapeutic efficacy (De Clercq & Field, 2006). Alternatively, microemulsions and self-emulsifying drug delivery systems were also attempted to augment the oral bioavailability of acyclovir (Cortesi & Esposito, 2008; Paul et al., 2013). Despite all these efforts, the successful oral therapy of acyclovir remains elusive.

The poor efficiency of acyclovir in oral therapy is mainly due to its limited aqueous solubility and low permeability (Fletcher & Bean, 1985; Wagstaff et al., 1994; Friedrichsen et al., 2002; Bergstrom et al., 2003). The biopharmaceutics classification system (BCS) has categorized acyclovir under class 3 considering the highest possible strength up to 400 mg. However, this drug is also available at a high dose of 800 mg and falls under BCS class 4, suggesting that a distinct classification for this drug is not possible with the BCS

Address for correspondence: Anroop B. Nair, Assistant Professor, Department of Pharmaceutical Sciences, College of Clinical Pharmacy, King Faisal University, P.O. 400, Al-Ahsa-31982, Kingdom of Saudi Arabia. Tel: +966 536 219 868. Email: anair@kfup.edu.sa

Keywords

Acyclovir, bioavailability, dissolution, hydroxypropyl-\(\beta\)-cyclodextrin, pharmacokinetics

History

Received 30 August 2013
Revised 5 October 2013
Accepted 5 October 2013
Oral buccoadhesive films of ondansetron: Development and evaluation

Rachna Kumria, Vishant Gupta, Sanjay Bansal, Jyoti Wadhwa, and Anroop B Nair

Department of Pharmaceutics, Swift College of Pharmacy, Ghaugar Sarai, Raipur, Punjab, India
1Department of Pharmaceutics, M. M. College of Pharmacy, Maharishi Markandeshwar University, Mullana, Ambala, Haryana, India
2Department of Pharmaceutics, Mehr Chand Polytechnic College, Jalandhar, Punjab, India
3Department of Pharmacy, Banasthali University, Banasthali, Jaipur, Rajasthan, India
4Department of Pharmaceutical Sciences, College of Clinical Pharmacy, King Faisal University, Al-Ahsa, Saudi Arabia

Address for correspondence: Dr. Rachna Kumria, Department of Pharmaceutics, Swift College of Pharmacy, Ghaugar Sarai, Raipur, Punjab, India. E-mail: Kumria_r@yahoo.com

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Abstract

Introduction:

Difficulty or inability in swallowing tablets/capsules during or after chemotherapy is common due to chemotherapy induced nausea and vomiting in patients. Buccoadhesive films of ondansetron hydrochloride were prepared for the prevention and treatment of chemotherapy-induced emesis. Films of varying polymeric composition were prepared in order to facilitate initial as well as prolonged drug release that could take care of acute as well as delayed emesis.

Materials and Methods:

Bucoadhesive films were prepared using polymers such as hydroxypropyl methylcellulose (HPMC) E5, HPMC K100, and Eudragit® NE 30 D. The effect of concentration of these polymers on physical properties and drug release were studied. All the films were prepared by solvent casting method. In another part of the study, the effect of drug concentration on physical and bucoadhesive properties of film were assessed, keeping the polymer concentration fixed.

Results:

Films containing HPMC showed good mucoadhesion. Increasing the concentration of Eudragit® NE 30 D in the films retarded drug release and increased residence time, however, reduced mucoadhesion. At a fixed polymer concentration and ratio, films prepared using an increased drug content showed an increased mucoadhesion.

Conclusion:

Films prepared using HPMC E5 (1000 mg), HPMC K100 (500 mg), and Eudragit® NE 30 D (750 mg) provided initial rapid followed by sustained drug release over a period of 6 h. Given the promising results, the study concluded that the developed buccal films have the potential to release ondansetron required for chemotherapy induced acute and delayed emesis.

Keywords: Buccoadhesive, Eudragit®, hydroxypropyl methylcellulose, mucoadhesion, ondansetron, permeation

INTRODUCTION

Oral route of drug delivery remains most popular route in drug delivery. Most of the dosage forms are