Development of Modified Release Nicotine Tablet Formulation for Treatment of Ulcerative Colitis

Marwan Y. Al-hurr*

Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq.

Abstract

One of the therapeutic effects of nicotine is used as a protective against developing ulcerative colitis. Ulcerative colitis is an inflammatory disease of the bowel affecting the superficial lining mucosa in the rectum and large intestine. In this study nicotine tablets were formulated as modified release tablets targeted to the colon. All formulas were studied for drug release, effect of diluent, retardant concentration, avicel grade, and compression force, the selected formula was then further studied for drug release in 3 different pH (coated tablets). The kinetic study revealed acceptable shelf life. Finally the selected formula was given to 6 patients in a pre-liminary clinical study which showed that nicotine can stabilize mild to moderate ulcerative colitis attacks.

Key words: Ulcerative colitis, Nicotine, Modified release, Colon delivery.

Introduction

Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local disease associated with the colon like Crohn’s disease, ulcerative colitis and irritable bowel syndrome, etc., but also for the potential systemic delivery of proteins and therapeutic peptides. The large intestine, though difficult to reach by preoral delivery is still deemed to the delivery of agents to cure the local disease of the colon (1,2). Colonic delivery formulations are in general may be designed to provide either the burst release or for sustained/prolonged release once reaching the colon (3). The proper selection of a formulation approach depends upon several important factors (4) which are: the pathology and pattern of the disease, the physicochemical and biopharmaceutical properties of the drug and finally the desired release profile of the active ingredient. The most common physiological factors considered in the design of delayed release colonic formulations is pH gradient of the gastrointestinal tract (5,6), delayed release formulations such as single unit or multiparticulate system for colon targeting, nanoparticulate system, microspheres, pelletsand beads, coating with pH sensitive polymers, embedding in matrices and bioadhesive systems (7) can be considered for

the design of colon delivery formulations. A wide array of polymers has been employed as drug release retarding agents each of which presents a different approach to matrix concept. Plastic matrix system, due to their chemical inertness and drug embedding ability, have been widely used for sustaining the release of drugs. Plastic polymers e.g. ethylcellulose and acrylates, which are capable of forming insoluble or skeleton matrices, have been widely used for controlled release of drugs due to their inertness and drug embedding ability. Acrylate polymers are widely used as tabletingcoating and as retardants for drug release in sustained release formulations (8). Ulcerative colitis (U.C) is an inflammatory disease of the bowel affecting the superficial lining mucosa in rectum and large intestine. The disease typically starts from the rectum and continues through the large bowel sparing the deeper layers of the intestinal wall (9). A variety of anti-inflammatory, immunosuppressive, and biological agents have been used to induce and maintain remission in UC. Sulfasalazine, olsalazine, balsalazide, oral and rectal mesalazine and topical corticosteroids are the standard first line therapies for UC. Patients who fail to respond to these agents are usually treated with oral corticosteroids.

*Corresponding author E-mail: m@marwanpharm.com, mngateway2000@yahoo.com
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There is a need for additional first line treatments in patients with UC and for alternatives to corticosteroid therapy in refractory patients. Nicotine may be such an agent for which smoking protects against the development of UC and controlled clinical trials have demonstrated that transdermal nicotine is efficacious for active UC\textsuperscript{10-15}. Nicotine is a drug obtained from the plant *Nicotina tabacum*. It’s a weak base. Its most preferred that smoking protects against the development of UC\textsuperscript{10-15}. Nicotine is efficacious for active UC\textsuperscript{16}.

Materials and Method

Nicotine (Sigma) gifted from Pharmacognosy Department, College of Pharmacy/ University of Baghdad, Sodium hydroxide (Fluka chemie AG. Buchs/Scheiz), Dibutylphthalate ( USB, B. Brussels,Belgium), Hydrochloric acid , Iosproanol, and Orthophosphoric acid (Riedal De Haen Ag Seele Hanover), Polyvinylpyrrolidone ( PVP K30 ), Acetone, Potassium dihydrogen phosphate, Ethanol 99% ( BDH chemicals, Ltd, Liverpool, England )Microcrystalline cellulose- Avicel\textsuperscript{®} - PH101, PH302, PH200 (FMC Corporation, Pennsylvania, USA), Eudragit\textsuperscript{®} L100, S100, RS PM – Rhôm Pharma GmbH Weiterstadt, Germany),Trisodium phosphate, Talc (Hopkins and Williams Ltd. England), coloring agent ( deep orange lakes) Zinc stearate (Barlocher, GmbH, Germany), Disodium hydrogen phosphate, Mannitol, Starch ( Merk, Germany). Table (1) summarizes 8 formulas to prepare modified release nicotine tablets by wet granulation method with alcohol. A known weight of the granules were mixed with a specified amount of Zn stearate ( 1% ) in a well closed container and compressed into tablets using 9mm punches ( tablet machine single punch – Korch, type EKO, Erweka GmbH, Kr Offenbanch/ Germany ).

<table>
<thead>
<tr>
<th>Constituents</th>
<th>Formulas ( mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Nicotine</td>
<td>20</td>
</tr>
<tr>
<td>PVP (10%)</td>
<td>20</td>
</tr>
<tr>
<td>Avicel\textsuperscript{®} PH302</td>
<td>40</td>
</tr>
<tr>
<td>Eudragit\textsuperscript{®} RS PM</td>
<td>20</td>
</tr>
<tr>
<td>Starch</td>
<td>100</td>
</tr>
<tr>
<td>Zinc stearate</td>
<td>1%</td>
</tr>
<tr>
<td>Mannitol</td>
<td>100</td>
</tr>
<tr>
<td>Avicel\textsuperscript{®} PH101</td>
<td>40</td>
</tr>
<tr>
<td>Avicel\textsuperscript{®} PH200</td>
<td></td>
</tr>
<tr>
<td>Compression force</td>
<td>4Kg</td>
</tr>
<tr>
<td>Total weight of final tablet</td>
<td>200</td>
</tr>
</tbody>
</table>

Evaluation of the prepared tablets

The following parameters were used to compare the prepared formulas to obtain the final selected formula.

1. Effect of diluents type on the percent released of nicotine.

Formula 1 and 2 were used to study the effect of two different diluents ( starch andmannitol ) on drug release.

2. Effect of Eudragit RS PM concentration.

Formula 1,3 and 4 were utilized to study the effect of different concentrations (10% , 20% and 30% respectively) of Eudragit RS PM on the drug release.
3. **Effect of Avicel grade.**
Formulas 1, 5 and 6 which contain Avicel PH 302, PH 101 and PH 200 respectively were used to study the effect of different grades of Avicel as channeling agent on the drug release.

4. **Effect of compression force on nicotine release.**
Formulas 1, 7 and 8 were used to study the effect of changing the compression force 4Kg, 6Kg and 8Kg respectively on the drug release.

**Drug release** : ( USP dissolution apparatus type II, Copley scientific Ltd, England).

The Medium used : pH 6.8 phosphate buffer 750ml, Apparatus II, rotation 75 rpm, with a Sampling time: 1, 2, 3, 4 and 6hr. The amount of nicotine dissolved was determined spectrophotometrically at λ<sub>max</sub> : 260nm of filtered samples. (UV visible spectrophotometer, Carrywin UV, Varian, Australia). The samples were diluted with dissolution medium if necessary and compare with a standard solution having a known concentration of nicotine in the same medium.

**Assay: HPLC analytical method**

The chromatographic separation was achieved on a C-18 column with UV detection at 260nm the HPLC system comprised a (Waters 1500 series HPLC pump USA), Waters 2487 dual λ absorbance detector, water breeze soft ware.) was operated at ambient temperature and used citrate buffer: methanol (85: 15 % v/v) with an apparent pH 2.4 as the mobile phase. The flow rate was maintained at 0.7 ml / min. and the retention time 6.94 min.<sup>18</sup>

**Preparation of coating formula**

The coating solution was prepared according to the Rhom pharma recommendations (the manufacturer) as follows:

**Formula :**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit (L 100 and S 100)</td>
<td>6gm</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>115.7gm</td>
</tr>
<tr>
<td>Acetone</td>
<td>77.1gm</td>
</tr>
<tr>
<td>Dibutylphthalate</td>
<td>1.2gm</td>
</tr>
<tr>
<td>Talc</td>
<td>3.25gm</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.25gm</td>
</tr>
<tr>
<td>Color</td>
<td>0.25gm</td>
</tr>
<tr>
<td>Titanium oxide</td>
<td>1.55gm</td>
</tr>
<tr>
<td>Semithicone</td>
<td>Q.S.</td>
</tr>
</tbody>
</table>

*mixture of Eudragit L 100 and S 100 in a ratio 1:2

The final coating solution formula prepared was 205.3gm.

**Procedure**

The formula was prepared by mixing the solvents together with the plasticizer (dibutylphthalate) in a high sheiner mixer MLW type LR10 (VEB ML W Prufgerate-werk, Medingen/ Stizfrtal/ Germany). Eudragit mixture was added slowly at room temperature, the powder was thoroughly wetted and care was taken to ensure that nothing settled at the bottom or formed lumps. mixing lasted for at least 30mins, until the solution was clear, the fillers were added step by step.

**Calculation of the amount of lacquer required**<sup>19</sup>

A specific thickness of coating is required based on the purpose of the coating and the amount needed depending on the surface area of the cores which may be calculated from the following equation assuming that the tablets are cylindrical in shape:

\[
S.A = \frac{\pi (d.h + \frac{1}{2} d^2)}{w} 
\]

Where d is the diameter (mm)

h is the height (mm)

S.A is the surface area (mm<sup>2</sup>)

The nicotine tablets had a diameter of 9mm and a surface area approximately equals to 240mm<sup>2</sup>. Since 3-5mg lacquer / cm<sup>2</sup> of tablet cores required to produce a core resistant to acidic environment (enteric coated tablets). So multiplying the surface area of the tablet core by the amount required and dividing it by the weight of tablet, the quantity of the lacquer to be applied as a percentage will be obtained.

The amount to be applied

(% dry lacquer substance)= S.A (mm<sup>2</sup>)/ w (mg) x (mg/mm<sup>2</sup>)

= 240 / 200 x 5

= 6%

**Tablet coating**

The selected Formula was coated by dipping method, each tablet was held by forcipes and dipped in the coating lacquer in and out 15-20 times, the coat was dried by a stream of warm air between each dip.<sup>20</sup>

**Dissolution study of the coated tablets**<sup>21</sup>

The dissolution rate of the selected formula for nicotine (coated tablets) was determined using USP apparatus at 37±0.5°C with paddle and the rotation speed was set at 75rpm in order to simulate the pH change of
the GIT, pH change dissolution procedure was applied as follows: 2hr. testing in 0.1N HCl solution followed by testing for one hour in phosphate buffer pH 4 obtained by adding 195ml 0.2M tribasic sodium phosphate solution during which samples were withdrawn at specified times and replaced immediately by fresh medium. Then the medium was changed to pH 6.8 by adding 55ml 0.2 M tribasic sodium phosphate adjusted by 2N NaOH or 2N HCl if required. samples were withdrawn at different time intervals and analyzed spectrophotometrically at 260nm.

Kinetic study
Effect of temperature:
The effect of temperature on the degradation of the selected formula of nicotine modified release tablets was studied. The study was done by storing 90 tablets in ovens (Mermert UL 80 ( Rostfrei, Schwach, Germany) at different temperatures 50°C, 60°C and 70°C. Samples were taken at specified time intervals and analyzed for nicotine. Since the degradation of the drug follows 1st order kinetics, the expiration date \( t_{10\%} \) at 25°C could be calculated using the following equation :

\[
T_{10\%} = 0.105/ k_{25 \text{°C}}
\]

Pre-liminary clinical study
Before giving the preparation we obtained a written consent of the patients who were included in this study. The modified release nicotine tablets of the selected formula was given to 6 patients suffering from mild to moderate ulcerative colitis (high mucus secretion, irritable bowel syndrome, mild to moderate bleeding and gases). All patients were put on 20mg single dose of nicotine for 2 weeks. The patients were evaluated clinically (physical examination and endoscopy) before and during treatment (physical examination) under the supervision of Dr. Mumtaz k. Hanna at his private clinic.

Results and discussion
Effect of diluent’s type on nicotine release
Although diluents are normally thought to be inert ingredients they can significantly affect the biopharmaceutical, chemical and physical properties of the final tablets. Formulas 1 and 2 which contain maize starch and mannitol as diluents, it was seen that starch gave the best drug release compared with mannitols shown in fig. 1. This behavior may be attributed to the swellability property of starch when compared with mannitol which the release is due to water solubility.

Effect of Eudragit concentration:

Eudragit RS PM can be incorporated in a percent of 10-30% (w/w) by weight to provide suitable granules and matrix tablets. The amount of Eudragit RS PM to be added, depends upon the solubility characteristics of the drugs and the rate required and the amount of Eudragit (as a retardant) respectively were evaluated. formula 1 gave the best modified release of nicotine when compared with the requirements of drug release to the colon. The results from dissolution profiles of formulas 1, 3 and 4 indicates that the retardant content affects the release of nicotine from the tablet, this result is in a consistent with the results obtained when Eudragit RSPM polymer was used as a retardant material for diclofenac sodium and indomethacin tablets. It appears that the amount of retardant needed is 10 % as shown in fig. 2. This is in agreement with the reported data which indicated that the retardation effect on the release of drug is dependent on the amount of Eudragit included.

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Figure 1: Effect of diluent type on the release of nicotine at pH 6.8 and 37°C

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Figure 2: Effect of Eudragit RS PM concentration on the percent released of nicotine at pH 6.8 and 37°C.
Effect of Avicel grade

Avicel is microcrystalline cellulose, it is partially depolymerized cellulose obtained as a pulp fibrous plant material with acids. The grade of Avicel depends on its normal loss on drying, bulk density and degree of polymerization values. The results showed that formula 1 in which Avicel PH 302 present, gave the best dissolution profiles while the difference in the release that occurred in the other formulas 5 and 6 which contain Avicel PH 101 and PH 200, respectively. is due to the difference in the porosity, surface area, particle size and density of Avicel as stated as shown in fig. 3

Coating formula

The tablets showed good appearance with no signs of cracking or splitting or peeling. Induction of hydrophobic materials and inert fillers (Mg stearate, talc, titanium oxide, aluma lakes with an orange color) these fillers facilitate processing of the lacquer by reducing its stickiness, help to smooth the permeability to water and decrease the tackiness of the drying lacquer. In addition they reduce the permeability of the film as long as the mechanical strength is maintained thereby enhancing the enteric properties of the film. Formula 1 was coated to target the drug to the colon. The coated tablets showed no drug release in 0.1 N HCl for 2hr. period of the test and the release of the drug increased rapidly when the pH changed to 6.8 as shown in fig 5.

Kinetic study

Effect of temperature

The stability of the coated modified release tablets were studied at different exaggerated temperatures (50 °C, 60 °C and 70°C) for 3 months. Fig 6 shows the change in the log percentage remaining of nicotine versus time at different temperatures. The obtained profiles were linear, indicating that nicotine degradation follows 1st order kinetics. The slopes of these lines were determined and the calculated rate constants (k) are summarized in fig (6). Arrhenius plot was then constructed as shown in fig 7. The linearity of the curve indicates its utility in predicting the rate of degradation at lower temperatures. since the degradation of the drug followed 1st order kinetics the expiration date can be calculated at 25 °C for nicotine coated matrix tablets and it was 52 month.
Clinical study
Nicotine was given to 6 non-smoking patients (5 males and 1 female) with an age range of 27-65 yr. The patients took 20mg once a day for 10 days suffering from mild to moderate ulcerative colitis. The outcome of this preliminary study indicates that 67% (4 out of 6 patient) were responsive to nicotine therapy (relief of bleeding and most signs and symptoms) although all patients suffered from an adverse effect reaction towards nicotine therapy because the patient were non smokers (light headedness or dizziness, nausea, headaches, central nervous system stimulation and tachycardia). Further studies in the future should be done including in vivo nicotine blood concentration to optimize the dose.

References


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