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Effect of CO_2 laser irradiation on Eudragit® L100-55, L100, and S100 coatings to modify drug release

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ABSTRACT

The aim of this work was to investigate the use of carbon dioxide (CO_2) laser irradiation to modify three types of pH-dependent Eudragit® (L100-55, L100, and S100) enteric coats with the aim of modulating drug release kinetics from the tablet cores. CO_2 laser irradiation causes rapid melting and resolidification/vaporization of materials locally and precisely through the absorption of infrared energy and so can potentially disrupt the barrier integrity and function of enteric coats. It was successfully utilized to shorten the lag time of drug release ($T_{50\%}$ and $T_{80\%}$) during dissolution testing. These changes were mainly caused either by pore formation on the surface of the coating and/or loosening of the film coat. In addition, changes in mechanical properties (Young's modulus and tensile strengths) and shifted IR peaks of the irradiated coatings were found, which correlated with drug release rates. This work is a proof-of-concept of tailoring drug release profiles by adjusting the power of the laser energy which could be useful for the modification of drug release for personalized medicines.

Keywords: Acrylic polymers, auto pH system, CO_2 laser irradiation, dynamic dissolution, Eudragit® coatings, modified drug release

INTRODUCTION

CO_2 lasers have the capability to operate continuously and with higher power outputs than earlier laser systems. It is a gas laser emitting an invisible beam of infrared energy with a wavelength of 10,600 nm, which is the highest wavelength of any of the commercially available lasers.[1,2] The popularity of CO_2 laser technology is because it is a very versatile tool; high-power CO_2 lasers (in the 2–6 kW range) are used in material processing applications such as cutting, welding, and drilling of sheet metal while low-power (below 100 W) CO_2 lasers are used in engraving and marking products.[3,4]

CO_2 lasers have also found wide medical application in brain tumor surgery, plastic surgery, sealing blood vessels, eye surgery, skin esthetics,[5-8] and increasing the topical delivery of substances with minimal skin damage.[9] In the pharmaceutical sector, CO_2 lasers have been used for drilling holes in coatings for osmotic controlled release tablets.[10] Further potential pharmaceutical applications are likely to benefit from the advantages of CO_2 laser irradiation in relation to high energy and high precision in a specific area through rapid heating, melting, resolidification, and/or vaporization.[11,12]

CO_2 laser technology is advantageous to laser ablation since the heat input is local, which means that the process is relatively fast and a narrow cut can be created, while only a small volume of the bulk is affected and no cutting force is required.[4,13] Nevertheless, the size and quality of the ablated area are dependent not only on optical and mechanical properties of the laser beam (thickness, gas composition, and pressure) and process parameters (laser power, laser speed, working distance, and mode of operation), which affect the energy density absorbed by the work material[14-17] but also the properties of the material[13,18] (thermal diffusivity and softening temperature).

Many polymers have high absorption, low reflectivity, and low thermal conductivity to the 10,600 nm wavelength. Consequently, the incident laser energy heats the polymer without high diffusion of energy into the adjacent surroundings. Different types and molecular masses of polymers have

different material behaviors toward CO_2 laser machining. The laser beam can either cause the disentanglement of the polymer chains or disrupt the integrity and breaks the chemical bonds of the polymers.[14,19-21]

Polymethyl methacrylates, acrylic polymers, have different properties, production processes, formulation, and/or additives which could affect their response to laser ablation.[13,22,23] In the pharmaceutical field, there are many types of acrylic polymers available on market including Eudragit® used as a coating agent targeting to different regions in the human gastrointestinal (GI) tract.[24-28]

The structure of an acrylic polymer determines many of its physical characteristics, such as glass transition temperature, melting temperature, mechanical properties, and level of thermal chain decomposition. CO_2 irradiation has been reported to play a key role in modifying properties of acrylic polymers; for example, Choudhury and Shirley[29] reported the carbon atom of the main chain restricts rotation of the chains on irradiation in the case of the methyl and methacrylate groups. Nimai[18] noted that small droplets of resolidified polymethyl methacrylate were left on the treatment zone with the low-molecular-weight grade, whereas pore formation was created on the surface of the high-molecular-weight polymeric workpiece. Jensen *et al*.[30] showed that the roughness of the irradiated polymethyl methacrylate varies depending on the chemical additives in each polymer grade. Romoli *et al*.[14] found that molecular weight had a great impact on the interaction between the polymer and CO_2 irradiation.

Eudragit® L100-55, L100, and S100 [Figure 1], acrylic polymers for enteric coating, enable pH-dependent release of the active ingredient to the duodenum, jejunum, and colon, respectively. Modified or localized release of drug in the intestine can be achieved by enteric coating that prevents drug release in the stomach, inhibiting drug degradation, and protecting the stomach from irritation, but which allows release at a specific site of the small intestine. The carboxylic groups of the polymers become ionized when exposed to the higher pH conditions of the small intestines, thus leading to dissolution of the coating and drug release. However, the rates of drug dissolution and tablet disintegration are dependent on several parameters, including the medium, drug, polymer properties (chemical structures and dissolution threshold), and mass transfer characteristics (diffusivity and diffusion layer) of the enteric-coated tablets.

Maximizing therapeutic efficacy for personalized medicine by being able to tailor drug release profile to the right site, at the right time, and the right dose could be better obtained and controlled with additional drug release mechanisms. Interindividual variability regarding pH, GI movement, GI fluid, and food intake is very common among patients. An auxiliary tool together with the fundamental pH-dependent drug release mechanism would give better benefit for individual patients. Applying new technologies, like CO_2 laser irradiation, allow physical modification of the enteric coating which then facilitates the drug release through the coatings alongside the pH-dependent mechanism. Novel oral solid dosage forms pairing with each patient's local disease with an approach to modify the dissolution of conventional enteric coatings in the environment mimicking the human GI tract could be fabricated.

The objective of this work was, therefore, to assess the effect of CO_2 laser irradiation to Eudragit® coatings on drug release modification using a dynamic dissolution model.[31-40]

MATERIALS AND METHODS

Materials

Eudragit® L100-55, L100, and S100 (powder form, referred to as L10055, L100, and S100) were donated from Evonik GmbH, Darmstadt, Germany. The dissolution pH threshold of the enteric polymers is 5.5, 6.0, and 7.0, respectively.[41] Triethyl citrate (TEC) was supplied by Sigma-Aldrich Co. Ltd., Dorset, UK. Talc (fine powder) was purchased from VWR International Ltd., Poole, UK. Prednisolone, a model drug, was purchased from Severn Biotech Ltd., Worcester, UK. Lactose was obtained from Ellis & Everard, Essex, UK. Cross-linked sodium carboxymethylcellulose (Ac-di-sol) was donated from FMC Biopolymer, Philadelphia, USA. Polyvinylpyrrolidone 44,000 and magnesium stearate were purchased from Sigma-Aldrich Co. Ltd., Dorset, UK.

Methods

Preparation of prednisolone tablets

Tablets were prepared as reported in previous publications.[42-44] The tablets contained 5% prednisolone, 88.5% lactose, 5% polyvinylpyrrolidone, 0.5% cross-linked sodium carboxymethylcellulose, and 1% magnesium stearate. Tablets were prepared by wet granulation. Cross-linked sodium carboxymethylcellulose was added both intra- and extra-granularly (50:50). Tablets were produced using a

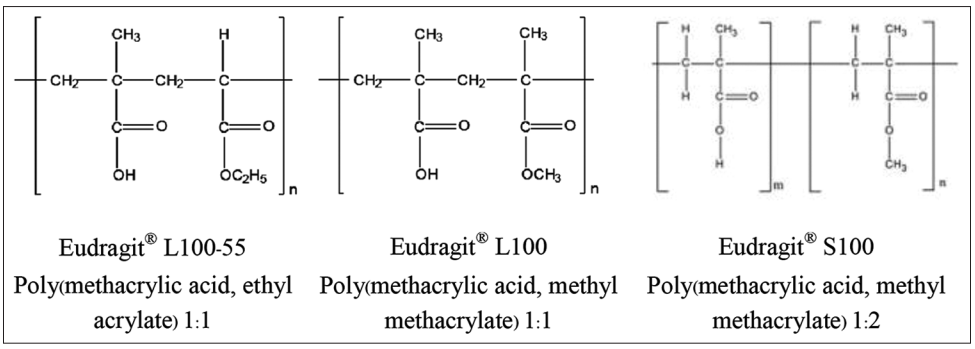

Figure 1: The chemical structure of Eudragit® L100-55, L100, and S100

single punch tableting machine (Manesty F3, Liverpool, UK), a biconcave 8 mm punch and die set (Holland Ltd., Nottingham, UK) to obtain 200 mg tablets containing 10 mg drug and crushing strength of 80 N.

Coating of prednisolone tablets

The recommended coating level for Eudragit® to achieve enteric properties on tablets is in the range of 4–6 mg pure polymer applied per square centimeter of tablets surface area (mg/cm^2).[41] Coatings were prepared as reported in the previous publications.[42-44] The enteric coating formulation was prepared from an organic polymer dispersion. The composition of the coating formulations was polymer weight 20 g and other materials as presented in Table 1. TEC was dissolved into water before mixing with organic solvent. Eudragit® powder was poured slowly into the above solution under stirring until a clear solution was obtained. Talc was added to the clear solution. Coating solutions were applied to prednisolone cores with a coating level of 5 mg/cm^2. Prednisolone tablets were coated using a Strea-1 bottom spray fluidized bed coater (Aeromatic AG, Bubendorf, Switzerland). The coating conditions were optimized and set to; inlet air temperature 40°C; outlet air temperature 32°C; fan capacity 15; atomizing pressure 0.2 bar; and spray rate 3.0 mL/min. After coating, tablets were fluidized in the coater for a further 15 min then dried at 40°C overnight and stored as control samples.

Preparation of film coats by solvent casting method

Organic films of Eudragit® L10055, L100, and S100 with TEC as a plasticizer were prepared by solvent casting in Teflon dishes (9 mL of solution in the dish). The cast films were air-dried until it was possible to remove them from the dishes, followed by drying at 50°C for 12 h to remove residual solvent.

Irradiation of tablet coats/film coats

A 40 W CO_2 deluxe hobby laser (Full Spectrum Laser LLC, Las Vegas, US) was used throughout this study to irradiate polymer coats (Eudragit® L10055, L100, and S100) on both sides of the coated tablets/one side of the films through a metal grid [Figure 2] with the laser settings; scanning speed (100%), power (40%), and resolution (high) at the focus length of 6.8 cm. An image of a square (3 cm × 3 cm) was created in the Corel Draw software and used as a template for all the 3 min irradiation runs in the Retina Engrave V4.01 software, which was used to control the laser. The laser beam was directed into the working field by a pair of mirrors and focused onto the sample by a focal lens and scanned over a two-dimensional area by the combined motion of X- and Y-axis.

Scanning electron microscopy (SEM)

The tablet surfaces, irradiated area, and cross-sections were examined using a scanning electron microscope (SEM, Quanta 200 FEG, FEI, the Netherlands). Samples were prepared by sputter coating with gold (Quorum model Q150, UK) for 3 min at 40 mA.

In vitro drug release in dynamic dissolution modeling

Drug release from irradiated coating prednisolone tablets was assessed using a USP-II apparatus (Model PTWS, Pharma Test, Hainburg, Germany). The tests were conducted in triplicate at 37 ± 0.5°C. A paddle speed of 50 rpm was employed. The tests were conducted under sink conditions. Tablets were tested for 2 h in 750 mL of 0.1 M HCl to simulate gastric residence time and subsequently transferred into 950 mL of modified Hanks (mHanks) bicarbonate physiological medium for 35 min from pH 5.6–7, then in 1000 mL of modified Krebs buffer (from pH 7 to 7.4 for 3.5 h and then to 6.5 h) to simulate the conditions of the duodenum, jejunum, and colon.[31-33,45,46] The mHanks buffer dissolution medium[45] (consisting of 136.9 mM NaCl, 5.37 mM KCl, 0.812 mM $MgSO_4.7H_2O$, 1.26 mM $CaCl_2$, 0.337 mM $Na_2HPO_4.2H_2O$, 0.441 mM KH_2PO_4, and 4.17 mM $NaHCO_3$) forms a modified Krebs buffer by adding 50 mL of pre-Krebs solution (consisting of 400.77 mM $NaHCO_3$ and 6.85 mM KH_2PO_4) to each dissolution vessel.[46]

The pH of the buffer is dynamically controlled and maintained by an auto pH system™,[33,47] which consists of a pH probe connected to a source of carbon dioxide gas (pH reducing gas), together with a supply of helium (pH increasing gas), controlled by a control unit. An equilibrium of a bicarbonate buffer is bicarbonate (HCO_3^-) and carbonic acid (H_2CO_3), coexisting with CO_2 (aq) which comes from dissociation of the carbonic acid. The buffer capacity (3.1, 3.4,

Table 1: Coating formulations

Formulations	Eudragit® L10055, L100, and S100
Polymer weight	20 g
Talc (anti-tacking)	10 g (50%[a])
Triethyl citrate (plasticizer)	2 g (10%[a])
Water	8.6 g (3%[b])
Isopropanol	279.4 g (97%[b])
Solid content of the spray suspension	10%

[a]Based on polymer weight. [b]Based on solvent weight

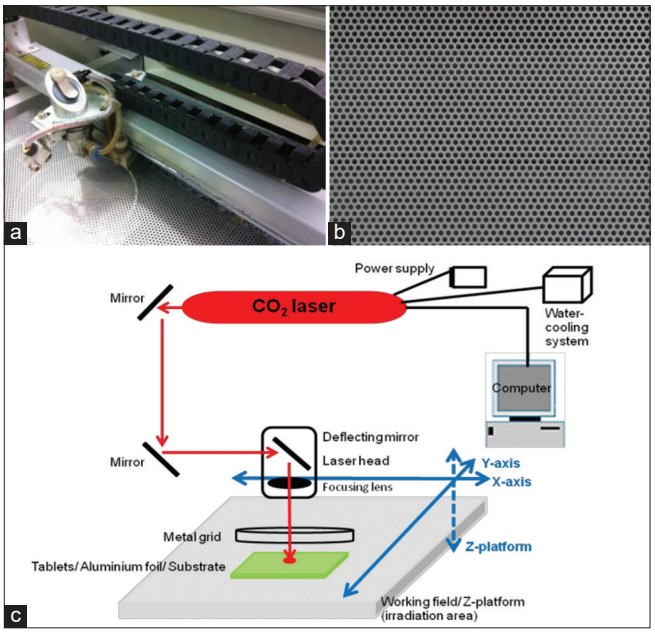

Figure 2: Laser head (a), metal grid (b), and schematic illustration of CO_2 laser irradiation system (c)

and 13 mM/L/ΔpH) and ionic composition of the physiological bicarbonate buffers closely resemble those of the intestinal fluids in the duodenum, jejunum, and colon in humans (3.2, 6.4, and 13 mM/L/ΔpH), respectively.[45,46,48-50]

The amount of prednisolone released from tablets coated with Eudragit® L10055, L100, and S100 was determined using an in-line UV spectrophotometer (Cecil 2020, Cecil Instruments Ltd., Cambridge, UK), with 5 min sampling intervals and a wavelength of 247 nm. Data were processed using Icalis software (Icalis Data Systems Ltd., Berkshire, UK). All samples had acceptable acid resistance as coated tablet products with <10% drug released in acid stage. The results are presented as mean ± standard deviation. The lag time is defined as the 1st time point which the percent drug release is greater than 10% ($T_{10\%}$), 50% ($T_{50\%}$), and 80% ($T_{80\%}$).

Film characterization

Tensile testing

The tensile strength and elastic (Young's) modulus were measured using an Instron Universal Testing Instrument Model 5567 (Instron Ltd, Norwood, USA), based on the ASTM D882-75d method. The film strips were cut to 8 mm × 24 mm and clamped between pneumatic grips. Five samples were tested at the strain rate of 10 mm/min and 100 N static load (2 kg). Data were analyzed using Bluehill software 2 (version 2.6).

Fourier transform infrared (FT-IR)

The molecular state of the film coating was obtained on a PerkinElmer spectrum model 100 FT-IR Spectrometer. The spectrum of an empty cell was used as the background. The scan was performed in the range of 4000 to 650 cm^{-1} for each sample at ambient conditions. Spectrum Express software (version 2008) was used to process the data.

RESULTS AND DISCUSSION

The SEM images compare the surface morphology and cross-section changes between the irradiated and conventional tablet coats [Figure 3]. It is apparent that higher irradiation caused a more uneven and porous surface in the irradiated tablet coat, while the control tablet had a smooth surface without pore formation. The laser/material interaction brings about surface melting, while the surface topography change is a direct result of melting and re-solidification.[51] Cross-sections showed sections of loose coating on the irradiated tablet coating layer while a rigid and compact coating was seen on the control. This is because laser irradiation induced the cleavage of the polymer back bone and side chain scission followed by the formation of bubbles or pores at the surface and in the volume of the film.[18,52]

The laser level applied has been reported to have an effect on surface wettability. Wang *et al*.[53] found, with high irradiation, the surface became hydrophilic, which may facilitate drug release from the irradiated polymeric coating. At this laser setting, the color of the irradiated coat tablets stayed the same as a non-charring process.[54] Nevertheless, over-irradiation could turn the treated coating to a brown color as the polymers tend to overheat or to interact with the substrate of the film or the film additives.

As shown in Figure 4, irradiation of the coated tablets altered the dissolution profiles. Interestingly, the lag time at $T_{10\%}$ remained the same between irradiated and non-irradiated

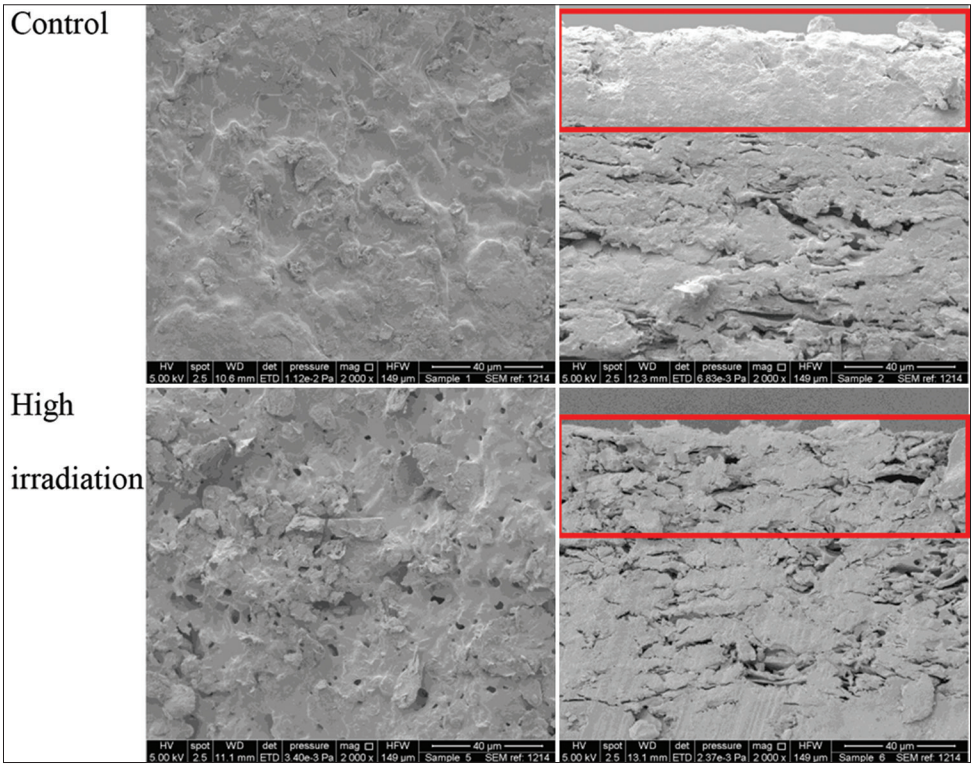

Figure 3: Scanning electron microscopy images of the surface morphology (left) and cross-section (right) of Eudragit®-coated tablets (×2000 resolution)

tablets following acid exposure. Meanwhile, the $T_{50\%}$ and $T_{80\%}$ values of the irradiated L10055, L100, and S100 coated tablet were much shorter [Figure 4, transparent bullet] than the control [Figure 4, solid bullet], suggesting that the release rate of the drug was faster at both 50% and 80% drug release. The same trend was found among the three types of Eudragit® coatings, which clearly demonstrate that the irradiation can shorten the lag time of drug release from coated tablets. The results from the SEM images [Figure 3] and dissolution profiles [Figure 4] confirm that irradiation to coating loosens the polymeric coat along with producing pore formation on the surface coating, which facilitates the drug to be released from the tablet core to GI simulated media.

In other words, irradiation treatment changes the degree of the film coalescence. The difference of the lag time at different percent drug release (10%, 50%, and 80%) between irradiated and control tablet had variable degrees [Table 2]. Klank *et al*.'s work[13] supports these dissolution outcomes in that the features of the laser-treated structures were subject to the polymer properties, particularly the thermal diffusivity and the decomposition mechanism. In terms of the chemical structure, Eudragit® L100-55 and L100 have similar main chain of methacrylic acid-co-acrylate [Figure 1] which had a strong effect of high laser irradiation with higher time difference (Δ) than Eudragit® S100 [Table 2]. This can explain why different types of Eudragit® give rise to different sensitivities to the CO_2 laser irradiation. Specific GI conditions like pH are present in pediatrics and geriatrics and/or certain GI disorders (e.g., gastroesophageal reflux disease). Therefore, modifying film coat and understanding drug release behaviors are likely to tailor the drug delivery for individual patients to the right site of action and at the right time.

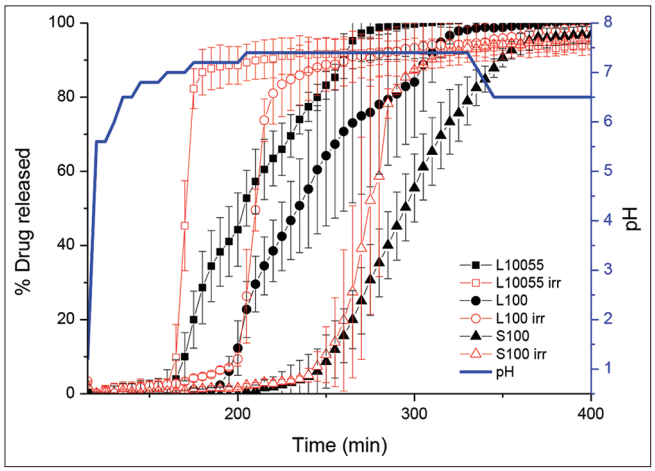

Figure 4: Drug release profiles of prednisolone comparing between the control coated tablets (black line with solid bullet) and irradiated tablets (red line with transparent bullet) among three different Eudragit® coatings: L10055 (square), L100 (circle), and S100 (triangle) in the auto pH apparatus

Notably, air bubbles were observed on the irradiated coats in the dissolution vessels. They have been reported to act as a transport barrier for the drug to leach out from the tablet cores.[55] Herein, the air bubbles did not have a significant influence on decreasing overall drug release rate. In terms of variability of drug release in each group, both irradiated and control tablets had high variation because the more subjective parameters in the dynamic dissolution setting were set up. Conventional dissolution testing commonly focuses on the pH only, unlike the auto pH system which has a number of underlying parameters representing the human GI tracts including various types of salt, pH step change, and buffer capacity.

CO_2 laser irradiation was postulated to change the interactions between polymer chains and the number of entanglements and thus changes the flexibility and the mechanical strength of the irradiated coats leading to a loosened film structure and enhanced permeability. As expected, Table 3 shows that high irradiation clearly resulted in a decrease in Young's modulus and tensile strength in all the three types of Eudragit®. The sharp drop of the Young's modulus values means that irradiated coatings had much less stiffness and elasticity. Meanwhile the drop of the tensile strength values suggests less capacity of the film to withstand exposed tension meaning that irradiated films are more easy to break during exposure to some force from the dissolution medium. The decrease in both Young's modulus and tensile strength caused a reduction of the lag time of irradiated tablets which could be ascribed to the drug diffusing through the porous and loose coating to the dissolution medium. Moreover, the degree of difference of mechanical values between the control and irradiated samples may imply various film behaviors correlating with different lag times among the three types of Eudragit®. Nevertheless, the biggest change in Young's modulus values found in S100 did not show the shortest lag time. Modification of chemical properties might then be used to interpret the degree difference.

FTIR spectra [Figure 5] with peaks at 1725 and 1695 cm^{-1} were characteristic of the C=O stretching of the ethyl or methyl acrylate and methacrylic acid, respectively.[56] Marked differences in the absorption of irradiated films were the two additional peaks at about 1805 and 1760 cm^{-1} corresponding to the stretching of the C=O bonds which are on the side chain of the molecules.[57-59] In addition, the increase in IR absorption at 1015 cm^{-1} assigned to the CH_3 bond was noticed among all

Table 2: The lag time (T, min) and time difference (**Δ**) comparing between control and irradiated coating tablets at three points of 10%, 50%, and 80% drug release

T at certain % drug release	Control L10055	Irradiated L10055	Δ*	Control L100	Irradiated L100	Δ*	Control S100	Irradiated S100	Δ*
$T_{10\%}$	50	45	5	80	80	0	135	130	5
$T_{50\%}$	85	50	35	115	90	25	175	155	20
$T_{80\%}$	125	55	70	170	100	70	215	170	45

*Time difference from the control

Table 3: Mechanical properties of irradiated L100-55, L100, and S100 films compared to the free films (control)

Sample	Film condition	Young's modulus (MPa)	Δ	Tensile strength (MPa)	Δ
L10055	Control	1489.67±168.99	673.20	20.48±2.87	17.39
	Irradiated	816.47±189.63		3.09±0.02	
L100	Control	1832.22±199.05	1134.51	14.28±3.70	10.87
	Irradiated	697.71±171.26		3.41±0.76	
S100	Control	2107.13±120.47	1608.90	19.50±4.96	17.85
	Irradiated	498.23±123.52		1.65±0.86	

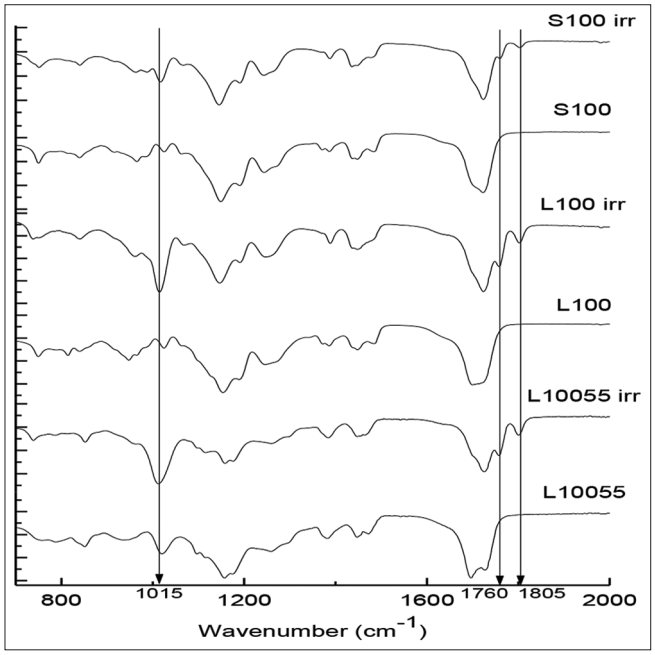

Figure 5: FTIR spectra of irradiated L10055, L100, and S100 films compared to the free films (control)

Eudragit® polymers.[60] Soeriyadi *et al*.[61] showed that thermal and photo degradation susceptibility in high-molecular-weight acrylic polymers monitored on a molecular level of surface changes was directly associated with the length of the ester side chain group. Consequently, the ethyl side chains in L10055 presumably had a pronounced influence on the shortest lag time of the dissolution profile. Conversely, both L100 and S100 have methyl ester side groups and hence have longer lag time. In addition, Chiantore *et al*.[62] found that acrylate units are more reactive than methacrylate meaning that the acrylate of L10055 is likely to be more sensitive to irradiation, leading to faster drug release compared with the methacrylate of L100 and S100.

The change in IR absorption of irradiated films indicates chemical changes of L10055, L100, and S100 after high irradiation corresponding to the previous work. In general, at elevated temperature and intense photo exposure, acrylic polymers go through depolymerization to monomer and ester decomposition forming methacrylic acid units, volatile molecules, and olefin.[61-63] In addition, chemical modification of the polymethyl methacrylate surface has been found under two competing reactions, namely, the scission and cross-linking,[58-59] although scission is predominant on strong irradiation.[64]

It is possible that apart from the change in the morphology of the film coats, the species produced by the strong laser process would react with the dissolution medium, leading to the acceleration of the drug release profiles. Besides, the chemical modification by high irradiation is likely to cause disruption of the polymer-polymer interactions which can increase the propensity for the dissolution medium to imbibe into the films, thus resulting in an increased dissolution rate. Davis *et al*.[65] demonstrated that differences in the chemical structure, such as the polymer backbones and the degree of substitution, led to distinct dissolution profiles.

Proposed Mechanisms for Modified Release Tablets Prepared by CO_2 Laser Irradiation

CO_2 laser irradiation induces heating and reactions of the polymer substrate which are considered to be ablation pathways (vaporization or removal of polymers). The chromophores along the polymeric chains of the coat absorb sufficient energy from the laser irradiation. The absorbed energy is associated with infrared photons, electronic excitation and induces molecule stretching and bending, and hence is converted into internal friction and heat. Therefore, the surface temperature increases due to the high-power density of the focused incident laser beam radiation, thereby achieving a high degree of ionization and/or promoting high surface mobility and resulting in the melting and decomposition of the polymer.[4,13,51,66,67] Loose polymer coats are then formed around the tablet. This irradiated layer of the polymeric coat is likely to facilitate the higher permeability and buffer influx toward the tablet core leading to the diffusion of the drug through the pores in the coatings, thus assisting in its dissolution.[44,68,69]

In principle, two simultaneous stages are involved in the polymer dissolution process; the polymer, which contains a free volume in the form of holes of molecular dimensions, absorbs solvent (solvent diffusion) to form a gel-like swollen layer with extensive cracking, and the swollen/cracked polymer chains disentangle into the solution (chain disentanglement) with reduction of the polymer layer thickness.[70,71] These findings agree well with the report from Gurny *et al*.[72] explaining that the two main mechanisms of drug release from porous and hydrophobic polymers are dissolution controlled and diffusion controlled. Thus, as mentioned earlier, it can be summarized that three factors determining the dissolution rate of the loaded drug are as follows: (1) The polymer dissolution medium interactions, (2) the structure and the porosity of the solid membrane, and (3) the physical status of the drug distributed in the dosage form.

Accordingly, the fact that the irradiated coated tablets had a faster dissolution rate can be attributed to the following reasons: (1) The irradiated polymer dissolution medium interactions are higher than the irradiated polymer-polymer attraction forces so that the irradiated polymer can absorb the solvent molecules rapidly and (2) irradiation offers a greater surface area and porosity for the coat to absorb the dissolution medium, allowing diffusing into the inner part of the tablets, and causing the polymer and tablet excipients to be swollen and disentangled and the dissolved prednisolone to release into the bulk dissolution medium.

CONCLUSION

CO_2 laser irradiation has the potential to modify drug release behaviors. The novel irradiated coated tablets showed faster dissolution with much less lag time under the pH condition, ionic composition, and buffer capacity mimicking the GI tract compared with conventional enteric coatings. The modification was mainly attributed to the change in surface morphology (porosity and rigidity), polymer network arrangement of locally irradiated enteric coats, change in Young's modulus, and tensile strength values. The irradiation process altered physicochemical and mechanical film properties including hardness, toughness, and extendibility, which influence drug diffusion and dissolution mechanisms, and thus the drug release behavior, compared with those of the untreated tablets. The Eudragit® L100-55 coats had the greatest irradiation effect with the shortest lag time resulted from the more sensitivity of its side chain group. This study highlights the potential of modifying a promising oral delivery system in three types of Eudragit® coatings of tablets induced by CO_2 laser irradiation.

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REFERENCES

1. Patel CK. Continuous-wave laser action on vibrational-rotational transitions of CO_2. Phys Rev 1964;136:A1187.
2. Ozdemir M, Sadikoglu H. A new and emerging technology: Laser-induced surface modification of polymers. Trends Food Sci Tech 1998;9:159-67.
3. Premasundaran M, Dawar AL. History of Lasers. Laser Basics; 2015.
4. Dumitras DC. CO_2 Laser Optimisation and Application. CO_2 Laser and Micro-Fluidics. London: InTech; 2012. p. 436.
5. Choudhri O, Karamchandani J, Gooderham P, Steinberg GK. Flexible omnidirectional carbon dioxide laser as an effective tool for resection of brainstem, supratentorial, and intramedullary cavernous malformations. Neurosurgery 2014;10:34-45.
6. Skaat A, Goldenfeld M, Cotlear D, Melamed S. CO_2 Laser-assisted deep sclerectomy in glaucoma patients. J Glaucoma 2014;23:179-84.
7. Oh HS, Kim JS. Clinical Application of CO_2 Laser, in CO_2 Laser Optimisation and Application. London: InTech; 2012. p. 357-78.
8. Omi T, Numano K. The role of the CO_2 laser and fractional CO_2 laser in dermatology. Laser Ther 2014;23:49-60.
9. Hsiao CY, Sung HC, Hu S, Huang CH. Fractional CO_2 laser treatment to enhance skin permeation of tranexamic acid with minimal skin disruption. J Dermatol 2015;230:269-75.
10. Theeuwes F, Higuchi T. Osmatic Dispensing Device for Releasing Beneficial Agent. California, United States: Alza Corporation; 1974.
11. Titapiwatanakun V, Basit AW, Gaisford S. A new method for producing pharmaceutical co-crystals: Laser irradiation of powder blends. Cryst Growth Des 2016;16:3307-12.
12. Titapiwatanakun V, Tankul J, Basit AW, Gaisford S. Laser irradiation to produce amorphous pharmaceuticals. Int J Pharm 2016;514:282-9.
13. Klank H, Kutter JP, Geschke O. CO_2-laser micromachining and back-end processing for rapid production of PMMA-based microfluidic systems. Lab Chip 2002;2:242-6.
14. Romoli L, Tantussi G, Dini G. Experimental approach to the laser machining of PMMA substrates for the fabrication of microfluidic devices. Opt Laser Eng 2011;49:419-27.
15. Eltawahni HA, Olabi AG, Benyounis KY. Assessment and Optimization of CO_2 Laser Cutting Process of PMMA. In: Chinesta FC, editor. International Conference on Advances in Materials and Processing Technologies. Pts One and Two; 2010. p. 1553-8.
16. Davim JP, Barricas N, Conceição M, Oliveira CA. Some experimental studies on CO_2 laser cutting quality of polymeric materials. J Mater Process Technol 2008;198:99-104.
17. Demian C, Costil S, Sallamand P, Soveja A., Liao L, Mattei S, *et al*. Laser densification of organic coating: Effects of laser wavelength, operating parameters and substrate properties. Surf Coat Tech 2012;206:3526-33.
18. Nimai CN, Lam YC, Yue CY, Sinha AT. CO_2 laser micromachining of PMMA: The effect of polymer molecular weight. J Micromech Microeng 2008;18:5020.
19. Caiazzo F, Curcio F, Daurelio G, Memola F, Minutolo C. Laser cutting of different polymeric plastics (PE, PP and PC) by a CO_2 laser beam. J Mat Process Technol 2005;159:279-85.
20. Rooks B. Laser Processing of Plastics. Vol. 31. United Kingdom: Emerald Group Publishing Ltd.; 2004. p. 338-42.
21. Mohan KL. Laser processing of polymers: An overview. B Mater Sci 1988;11:225-38.
22. Hong TF, Ju WJ, Wu MC, Tai CH, Tsai C, Fu LM. Rapid prototyping of PMMA microfluidic chips utilizing a CO_2 laser. Microfluid Nanofluid 2010;9:1125-33.
23. Prakash S, Kumar S. Fabrication of microchannels on transparent PMMA using CO_2 Laser (10.6 μm) for microfluidic applications: An experimental investigation. Int J Pr Eng Man 2015;16:361-6.
24. Goyanes A, Chang H, Sedough D, Hatton GB, Wang J, Buanz A, *et al*. Fabrication of controlled-release budesonide tablets via desktop (FDM) 3D printing. Int J Pharm 2015;496:414-20.
25. Varum FJ, Freire AC, Fadda HM, Bravo R, Basit AW. A dual pH and microbiota-triggered coating (Phloral™) for fail-safe colonic drug release. Int J Pharm 2020;583:119379.
26. Varum FJO, Freire AC, Bravo R, Basit AW. OPTICORE™, an innovative and accurate colonic targeting technology. Int J Pharm 2020;583:119372.
27. Ibekwe VC, Khela MK, Evans DF, Basit AW. A new concept in colonic drug targeting: A combined pH-responsive and bacterially-triggered drug delivery technology. Aliment Pharm Ther 2008;28:911-6.
28. Maroni A, Moutaharrik S, Zema L, Gazzaniga A. Enteric coatings for colonic drug delivery: State of the art. Expert Opin Drug Deliv 2017;14:1027-9.
29. Choudhury IA, Shirley S. Laser cutting of polymeric materials: An experimental investigation. Opt Laser Technol 2010;42:503-8.
30. Jensen MF, Noerholm M, Christensen LH, Geschke O. Microstructure fabrication with a CO_2 laser system: Characterization and fabrication of cavities produced by raster scanning of the laser beam. Lab Chip 2003;3:302-7.
31. Goyanes A, Hatton GB, Basit AW. A dynamic *in vitro* model to evaluate the intestinal release behaviour of modified-release

corticosteroid products. J Drug Deliv Sci Tec 2015;25:36-42.
32. Goyanes A, Hatton GB, Merchant HA, Basit AW. Gastrointestinal release behaviour of modified-release drug products: Dynamic dissolution testing of mesalazine formulations. Int J Pharm 2015;484:103-8.
33. Merchant HA, Goyanes A, Parashar N, Basit AW. Predicting the gastrointestinal behaviour of modified-release products: Utility of a novel dynamic dissolution test apparatus involving the use of bicarbonate buffers. Int J Pharm 2014;475:585-91.
34. Ong JJ, Awad A, Martorana A, Gaisford S, Stoyanov E, Basit AW, *et al*. 3D printed opioid medicines with alcohol-resistant and abuse-deterrent properties. Int J Pharm 2020;579:119-69.
35. Awad A, Fina F, Trenfield SJ, Patel P, Goyanes A, Gaisford S, *et al*. 3D printed pellets (miniprintlets): A novel, multi-drug, controlled release platform technology. Pharmaceutics 2019;11:148.
36. Fina F, Goyanes A, Madla CM, Awad A, Trenfield SJ, Kuek JM, *et al*. 3D printing of drug-loaded gyroid lattices using selective laser sintering. Int J Pharm 2018;547:44-52.
37. Robles-Martinez P, Xu X, Trenfield SJ, Awad A, Goyanes A, Telford R, *et al*. 3D printing of a multi-layered polypill containing six drugs using a novel stereolithographic method. Pharmaceutics 2019;11:274.
38. Xu X, Robles-Martinez P, Madla CM, Joubert F, Goyanes A, Basit AW, *et al*. Stereolithography (SLA) 3D printing of an antihypertensive polyprintlet: Case study of an unexpected photopolymer-drug reaction. Addit Manuf 2020;33:101071.
39. Goyanes A, Kobayashi M, Martinex-Pacheco R, Gaisford S, Basit AW. Fused-filament 3D printing of drug products: Microstructure analysis and drug release characteristics of PVA-based caplets. Int J Pharm 2016;514:290-5.
40. Goyanes A, Wang J, Buanz A, Martínez-Pacheco R, Telford R, Gaisford S, *et al*. 3D printing of medicines: Engineering novel oral devices with unique design and drug release characteristics. Mol Pharm 2015;12:4077-84.
41. Roehm E. EUDRAGIT Application Guidelines. 10th ed. Germany: GmbH, D; 2008.
42. Liu F, Lizio R, Meier C, Petereit HU, Blakey P, Basit AW, *et al*. A novel concept in enteric coating: A double-coating system providing rapid drug release in the proximal small intestine. J Control Release 2009;133:119-24.
43. Liu F, Basit AW. A paradigm shift in enteric coating: Achieving rapid release in the proximal small intestine of man. J Control Release 2010;147:242-5.
44. Varum FJ, Merchant HA, Goyanes A, Assi P, Zboranová V, Basit AW. Accelerating the dissolution of enteric coatings in the upper small intestine: Evolution of a novel pH 5.6 bicarbonate buffer system to assess drug release. Int J Pharm 2014;468:172-7.
45. Liu F, Merchant HA, Kulkarni RP, Alkademi M, Basit AW. Evolution of a physiological pH 6.8 bicarbonate buffer system: Application to the dissolution testing of enteric coated products. Eur J Pharm Biopharm 2011;78:151-7.
46. Fadda HM, Merchant HA, Arafat BT, Basit AW. Physiological bicarbonate buffers: Stabilisation and use as dissolution media for modified release systems. Int J Pharm 2009;382:56-60.
47. Merchant HA. *In-vitro*, *in-vivo* and *in-silico* Models in Oral Drug Delivery and their Relevance to Human Gastrointestinal Physiology. Doctor of Philosophy in Pharmaceutics. University of London: The School of Pharmacy, London; 2012.
48. Fadda HM, Sousa T, Carlsson AS, Abrahamsson B, Williams JG, Kumar D, *et al*. Drug solubility in luminal fluids from different regions of the small and large intestine of humans. Mol Pharm 2010;7:1527-32.
49. Varum FJ, Hatton GB, Basit AW. Food, physiology and drug delivery. Int J Pharm 2013;457:446-60.
50. Bratten J, Jones MP. Prolonged recording of duodenal acid exposure in patients with functional dyspepsia and controls using a radiotelemetry pH monitoring system. J Clin Gastroenterol 2009;43:527-33.
51. Waugh DG, Lawrence J. On the use of CO_2 laser induced surface patterns to modify the wettability of poly (methyl methacrylate) (PMMA). Opt Laser Eng 2010;48:707-15.
52. Rebollar E, Bounos G, Oujja M, Georgiou S, Castillejo M. Morphological and chemical modifications and plume ejection following UV laser ablation of doped polymers: Dependence on polymer molecular weight. Appl Surf Sci 2007;253:7820-5.
53. Wang ZK, Zheng HY, Lim CP, Lam YC, *et al*. Polymer hydrophilicity and hydrophobicity induced by femtosecond laser direct irradiation. Appl Phys Lett 2009;95:111110.
54. Snakenborg D, Klank H, Kutter JP. Microstructure fabrication with a CO_2 laser system. J Micromech Microeng 2004;14:182.
55. Ferrero C, Bravo I, Jiménez-Castellanos MR. Drug release kinetics and fronts movement studies from methyl methacrylate (MMA) copolymer matrix tablets: Effect of copolymer type and matrix porosity. J Control Release 2003;92:69-82.
56. Bajaj P, Goyal M, Chavan RB. Thermal behavior of methacrylic acid-ethyl acrylate copolymers. J Appl Polym Sci 1994;51:423-33.
57. Rebollar E, Bounos G, Oujja M, Domingo C, Georgiou S, Castillejo M. Influence of polymer molecular weight on the UV ablation of doped poly (methyl methacrylate). Appl Surf Sci 2005;248:254-8.
58. Beauvois S, Renaut D, Lazzaroni R, Laude LD, Bredas JL. Physico-chemical characterization of the effect of excimer laser irradiation on PMMA thin films. Appl Surf Sci 1997;109-110:218-21.
59. Torikai A, Hattori T, Eguchi T. Wavelength effect on the photoinduced reaction of polymethylmethacrylate. J Polym Sci Pol Chem 1995;33:1867-71.
60. Willis HA, Zichy VJ, Hendra PJ. The laser-Raman and infra-red spectra of poly (methyl methacrylate). J Polym 1969;10:737-46.
61. Soeriyadi AH, Trouillet V, Bennet F, Bruns M, Whittaker MR, Boyer C, *et al*. A detailed surface analytical study of degradation processes in (meth) acrylic polymers. J Polym Sci Pol Chem 2012;50:1801-11.
62. Chiantore O, Trossarelli L, Lazzari M. Photooxidative degradation of acrylic and methacrylic polymers. J Polym 2000;41:1657-68.
63. Özlem-Gundogdu S, Gurel EA, Hacaloglu J. Pyrolysis of of poly (methy methacrylate) copolymers. J Anal Appl Pyrol 2015;113 Suppl C:529-38.
64. Mitsuoka T, Torikai A, Fueki K. Wavelength sensitivity of the photodegradation of poly (methyl methacrylate). J Appl Polym Sci 1993;47:1027-32.
65. Davis M, Ichikawa I, Williams EJ, Banker GS. Comparison and evaluation of enteric polymer properties in aqueous solutions. Int J Pharm 1986;28:157-66.
66. Yuan D, Das S. Experimental and theoretical analysis of direct-write laser micromachining of polymethyl methacrylate by CO_2 laser ablation. J Appl Phys 2007;101:024901.
67. Prasad M, Conforti PF, Garrison BJ. On the role of chemical reactions in initiating ultraviolet laser ablation in poly (methyl methacrylate). J Appl Phys 2007;101:103113.
68. Garg A, Gupta M, Bhargava HN. Effect of formulation parameters on the release characteristics of propranolol from asymmetric membrane coated tablets. Eur J Pharm Biopharm 2007;67:725-31.
69. Herbig SM, Cardinal JR, Korsmeyer RW, Smith KL. Asymmetric-membrane tablet coatings for osmotic drug delivery. J Control Release 1995;35:127-36.
70. Nguyen DA, Fogler HS. Facilitated diffusion in the dissolution of carboxylic polymers. AIChE J 2005;51:415-25.
71. Miller-Chou BA, Koenig JL. A review of polymer dissolution. Prog Polym Sci 2003;28:1223-70.
72. Gurny R, Doelker E, Peppas NA. Modelling of sustained release of water-soluble drugs from porous, hydrophobic polymers. Biomaterials 1982;3:27-32.