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Influence of Pressurized Carbon Dioxide on Ketoprofen-Incorporated Hot-Melt Extruded Low Molecular Weight Hydroxypropylcellulose

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Abstract

Objectives—The aim of the current research project was to investigate the effect of pressurized carbon dioxide (P-CO_2) on the physico-mechanical properties of Ketoprofen (KTP)-incorporated hydroxypropylcellulose (HPC) (Klucel™ ELF, EF and LF) produced using hot melt extrusion (HME) techniques and to assess the plasticization effect of P-CO_2 on the various polymers tested.

Methods—The physico-mechanical properties of extrudates with and without injection of P-CO_2 were examined and compared to extrudates with the addition of 5% liquid plasticizer of propylene glycol (PG). The extrudates were milled and compressed into tablets. Tablet characteristics of the extrudates with and without injection of P-CO_2 were evaluated.

Results & conclusion—P-CO_2 acted as a plasticizer for tested polymers, which allowed for the reduction in extrusion processing temperature. The microscopic morphology of the extrudates were changed to a foam-like structure due to expansion of the CO_2 at the extrusion die. The foamy extrudates demonstrated enhanced KTP release compared to the extrudates processed without P-CO_2 due to the increase of porosity and surface area of those extrudates. Furthermore, the hardness of the tablets prepared by foamy extrudates was increased and the percent friability was decreased. Thus, the good binding properties and compressibility of the extrudates were positively influenced by utilizing P-CO_2 processing.

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Declaration of interest:

None of the authors report any conflict of interest in the context of this work.

Keywords

Hot melt extrusion (HME); pressurized carbon dioxide (P-CO_2); Ketoprofen (KTP); Hydroxypropylcellulose (HPC); Foamy extrudates

Introduction

Solubility is considerd one of the most important factors to determine the oral bioavailability of any active pharmaceutical ingredient (API)[1]. Over 40% of APIs are poorly water soluble and result in low oral bioavailability[2]. Thus, enhancement of the solubility and oral bioavailability of APIs has received much interest within the pharmaceutical research community. Various techniques are used to overcome the poor water solubilty of APIs such as salt formation, solubilization by cosolvents, particle size reduction, prodrug approaches, as well as the most successful one to date solid dispersion techniques[1]. Solid dispersion is defined as "The dispersion of one or more active ingredients in an inert carrier matrix at solid-state''[3]. There are many methods to prepare solid dispersions such as the fusion method, ball milling, solvent evaporation, lyophilization, hot melt extrusion (HME) and supercritical fluid methods[4, 5]

HME has received increasing attention in pharmaceutical industry over the last few decades as a beneficial technique to produce solid dispersions[6]. There are many advantages of using HME over the conventional pharmaceutical processing methods, such as it is a relatively fast continuous manufacturing process[7, 8] and it can convert an active pharmaceutical ingredients (API) into its amorphous state[9]. Moreover, another important advantage of HME is that no solvent is required, so it is considered a "green method" to enhance the solubility and oral bioavailability of poorly water soluble drugs[10, 11]. However, a concern of HME is drug and polymer degradation due to potential high processing temperature. Thus, in case of thermo-labile drugs, processing aids or plasticizers might be added to reduce the viscosity and lower the minimum processing temperature, thus decreasing both drug and polymer degradation[12]. Choice of plasicizers as a processing aid in HME depends on the compatibility between the drug and other excipients in the formulation. Use of plasticizers may affect the physico-mechanical properties and drug release profiles of the hot melt extrudates. Plasticizers often increase the elasticity and flexibility of the extrudates[12]. Some plasticizers adversely affect the storage stability of pharmaceutical formulations resulting in changes within their release profiles[13].

It has been reported that P-CO_2 can act as a reversible plasticizer and foaming agent[14]. CO_2 is non-toxic, non flammable and chemically inert in nature[15, 16]. These properties could increase the interest of the combination of P-CO_2 and HME[17]. Previous investigation have shown that P-CO_2 when injected during HME processing acts as a plasticizer for some pharmaceutically utilized polymers, such as Eudragit® E100, polyvinylpyrrolidone-co-vinylacetate 64 (PVP-VA 64) and ethylcellulose 20 centipoise (EC 20 cps), (allowing for a decrease in their T_g)[18] and thus, reduction in the extrusion processing temperatures[19–23]. Within an HME process, P-CO_2 changes the microscopic morphology of the extrudates to foam-like structures due to its expansion characteristics at the extrusion die[14, 24]. This

morphological change could result in increasing the surface area and porosity, thereby, enhancing the milling efficiency of hot melt extrudates[19, 25]. In the recent past, several studies have evaluated the effect of supercritical CO_2 on HME processing. However, limited studies have been conducted to study the effect of the pressurized (***subcritical***) state of CO_2. P- CO_2 entails more advantages than supercritical CO_2 such as being more economical since no pump is required.

Hydroxypropyl cellulose (HPC) is a non-ionic water soluble cellulose ether. It has many pharmaceutical applications such as an emulsion stabilizer, binder, film-former, thickner and drug carrier[26]. Typically, HPC extrudates may be difficult to mill due to its high elasticity and hygroscopicity[27]. An objective of this study is to resolve this potential issue.

In this current research study, the main objective was to evaluate the effect of P-CO_2 on ketoprofen (KTP) and HPC polymers using HME techniques. The model drug KTP is a non-steroidal anti-inflammatory agent and, it is crystalline in nature with poor water solubility. It is conventionally formulated as an oral dosage form[28]. It is thermally stable with a melting point of approximately 95°C and "burns out" over a temperature range of 235–400°C[29]. Indeed the literature has recently reported that hot melt extudates of KTP and HPC has demonstrated poor milling efficiency[30]. In order to solve these underlining issues, in the present study we investigated the effect of P-CO_2 on the physico-mechanical properties of KTP and HPC extrudates produced using HME techniques.

Materials

Klucel™ LF, EF and ELF hydroxypropylcellulose (HPC) and polyplasdone XL™ were obtained as gift samples from Ashland Inc (Wilmington, DW 19808 USA). Propylene glycol and Magnesium Stearate were purchased from Spectrum Chemicals (14422 S. San Pedro Street Gardena, CA 90248 USA). Ketoprofen was purchased from Parchem-Fine & specialty chemicals (415 Huguenot St, New Rochelle, NY 10801 USA). CO_2 was supplied in gas cylinders (pure clean) from Airgas (902 Rockefeller St, Tupelo, MS 38801 USA), Avicel®102 was received as a gift samples from FMC biopolymers (1735 Market Street, Philadelphia PA 19103 USA). Flow lac® 90 was received as a gift samples from Meggle USA Inc. (50 Main street, White Plains, NY 10606 USA). Aerosil® was obtained as a gift samples from Evonik degussa Corporation (379 Interpace Parkway, Parsippany, NJ 07054 USA). Syloid® was received from W. R. Grace & Co.- Conn (7500 Grace Drive, Columbia, MD 21044 USA). All other chemicals and reagents used in the present study were of analytical grade and obtained from Fisher scientific (Fair Lawn, NJ 07410 USA).

Methods

Thermogravimetric Analysis (TGA)

TGA studies were performed for KTP and polymers used in this study to determine their stability at the extrusion temperatures using a Perkin Elmer Pyris 1 TGA equipped with Pyris manager software (PerkinElmer Life and Analytical Sciences, 710 Bridgeport Ave., Connecticut, USA).

Differential Scanning Calorimetry (DSC)

DSC was obtained using Perkin Elmer Pyris 1 DSC equipped with Pyris manager software (PerkinElmer Life and Analytical Sciences, 710 Bridgeport Ave., Connecticut, USA). Appoximately 2–4 mg of KTP, physical mixtures or extrudates were heated from 30°C to 200°C at heating rate of 10°C/min.

Hot Melt Extrusion (HME)

The HME processes were performed using a twin-screw extruder (16 mm Prism Euro Lab, Thermo Fisher Scientific). The extruder is divided into 10-barrel segments adjacent to the gravimetric feeder. Thermo Fisher Scientific standard screw configuration was used for this study, which consists of four coveying segments and three mixing zones and all of the injections were made through the injection port at the conveying zones of the screw configuration. All of the formulations as mentioned in (Table 1) were extruded at maximum torque possible. The screw speed was 75 – 200 rpm at a temperature range from 90–140°C and, at a feed rate of ~ 0.7Kg/hr. The propylene glycol was injected in a barrel segment 4 using Watson-Marlow 520S IP31 Pump. CO_2 was pressurized and injected into the extruder using a high-pressure regulator connected to flexible stainless steel hose with armor casing. The other end of the hose was connected to the four-way connection, fitted with a pressure gauge, bleed valve, check valve (ball type for unidirectional flow of gas), with the later being connected to the injection port seating on the extruder in barrel segment 4 or 6 which are conveying zones (Figure 1). Metering of CO_2 was regulated using the regulator knob.

Light Microscopy

To evaluate the microscopic morphology of the extrudates with and without P-CO_2 injection and, with the addition of 5% PG, light microscope with camera was used. A thin transverse section (TS) of extrudates were placed on glass slides and observed under the microscope. Photographs of TS samples were taken with zoom power 3×.

Milling

The hot melt extrudates were milled and passed through ASTM mesh sieve #40 using a comminuting mill (Fitzpatrick, Model L1A).

High-Performance Liquid Chromatography (HPLC)

All samples were analyzed using a Waters HPLC equiped with Empower software to analyze the data. HPLC consisted of a Water 600 binary pump, Waters 2489 UV/detector, and Waters 717 plus autosampler (Waters Technologies Corporation, 34 Maple St., Milford, MA 0157). The column used was phenomenex luna C18 (5μ, 250 mm × 4.6 mm). The mobile phase constituted of acetonitrile/20 mMol phosphate buffer, 55:45 (%v/v) at pH 4[30, 31] at a flow rate of 1 ml/min and injection volume of 20 μl. The UV detetctor wavelength for KTP detection was set at 256 nm.

Tableting

The milled extrudates were used to prepare the tablet blends using microcystalline cellulose (Avicel®102) or lactose (flow lac® 90) as diluent, colloidal silicon dioxide (Arosil®) or

silicon dioxide (Syloid®) as flowability enhancer, polyplasedone XL™ as a disintegrant and magnesium stearate as a lubricant (Tables 2, 3). The placebo and 25 mg strength tablets were compressed with the same compression force (1.5–1.6 kN) on a manual tablet press using 8 and 10 mm biconcave punch to a final tablet weighing 175 and 350 mg, respectively. The tablet properties such as thickness, hardness, tablets drug content uniformity and percent friability were performed. A digital caliper was used to obtained the tablet thickness. Optimal control tablet hardness tester were used for the tablet hardness determination. The tablet's drug content uniformity were evaluated using HPLC analysis. The percent friability was calculated for each batch using a Vanderkamper friability tester by using by applying the following equation.

$$F = \frac{W1 - W2}{W1} \times 100$$

where F is percent friability, and W1 and W2 are the initial and final tablet weights, respectively.

In Vitro Drug Release

Extrudates equivalent to 25 mg KTP were filled in HPMC capsules and *in vitro* drug release profiles were performed using a USP type II dissolution apparatus. The dissolution media was 1000 ml 0.05 M phosphate buffer pH 7.4 and, was maintained at 37 °C. A sample volume of 2 ml were taken at time points 10, 20, 30, 45, 60 min.[32], filtered and analyzed using HPLC and 2 ml of fresh dissolution media were added back to the dissolution vessel at each time point. The release profiles of 25 mg KTP tablets were obtained in the same conditions.

Stability Study

All KTP/Klucel™ ELF, EF and LF extrudates with and without P-CO_2 injection were sealed in glass bottles and stored at 25°C/60% RH for three months. Recrystalization assessments were determined by DSC.

Results and Discussion

Thermal Analysis

TGA data demonstrated that all formulations utilized in this study were stable under the employed processing temperature (data not shown). DSC data showed that ketoprofen melting peaks at 90°C disappeared for all of the milled extrudates with and without P-CO_2 injection, which indicated the conversion of the crystalline form into the amorphous form. All milled extrudates remained in an amorphous form at the end of the last time point after 3 months of storage at 25°C/60% RH (Figure 2).

Hot Melt Extrusion

During extrusion with P-CO_2 injection, metering of CO_2 was controlled using the regulator until the reading on the pressure guage located at the 4-way connector was maintained between 75–150 psi. CO_2 was provided in a liquid form from a CO_2 gas cylinder (pure

clean). The back pressure from the injection port maintained the CO_2 in a liquid state that further dropped the temperature at the injection port as low as 2°C. The injection zone should be completely filled with the physical mixture for the formation of the melt seals to prevent any leakage of gas from the extruder and allow good mixing between the materials and CO_2. As described by Verreck *et al.*, 2007d, diffusion and dissolution of the injected P-CO_2 in the polymers manifested as extremely foamy extrudates with the increment of die swelling accompanied by CO_2 expansion at the terminal end of the die (Figure 3). As investigated by Repka *et al.*, HPC extrudates were more dense, flexible and hygroscopic[27]. While, upon injection of PG in zone 4, the extrudates were sticky and elastic. Injection of PG as a plasticizer reduced the extrusion processing temperature by about 30°C. However, the P-CO_2 can also act as a plasticizer which has been previously mentioned by Lyons *et al.*[23]. In formulations of k_4, k_5 and k_6 when P-CO_2 was injected in zone 4, the processing temperature decreased by about 20°C as compared to the processing temperature without injecting P-CO_2 (Table 4). These findings confirmed that CO_2 acts as a reversible plasticizer and escapes from the formulation at the end of HME processing and no more weight will be added to the formulation as shown by Verreck *et al.*[20]. Furthermore, CO_2 is chemically inert, so the compatibility issue of other plasticizers with the polymers and APIs used in the study, was avoided. Plasticization effect of CO_2 was not feasible when P-CO_2 was injected in zone 6 (formulation k_{10},k_{11}, and k_{12}) due to the short distance between zone 6 and the extruder die.

The microscopical images of the extrudates processed with P-CO_2 injection demonstrated higher surface area and porosity as compared to the extrudates processed without P-CO_2 injection and, the one with PG injection (Figure 4).

HPC extrudates typically are very difficult to be milled and a freezing process is required before the milling procedure[30]. Because of the high flexibility and hygroscopicity of the extrudates with PG injection, milling failing occurs due to the shut down of the Fitzmill as a result of generation of maximum torque (Figure 5). The phenomenon of milling failing on these extrudates with PG injection could not be improved even when the freezing process is used before the milling. Milling process is an essential step in the pharmaceutical industries and failing of this step will prevent any further processing into suitable dosage forms. A significant enhancement of the milling efficiency of extrudates with P-CO_2 injection was observed. The milling efficiency was determined by the torque value of the Fitzmill. As mentioned by Verreck *et al.*[19] these processing properties of the materials would provide numerous benefits during manufacturing of various solid dosage forms such as tablets and capsules.

Jeong *et al.* has showed that there is a lowering in bulk density of extrudates in presence of P-CO_2 injection[33]. Our results showed that foamed milled extrudates exhibited lower bulk density and tap density as compared to the extrudates without P-CO_2 injection, due to an increase in porosity and surface area of the extrudates (Table 5).

HPLC analysis confirmed that the drug content uniformity of KTP in all formulations were acceptable and within the range of 98–105%.

The *in vitro* dissolution profiles were performed to evaluate the KTP/ Klucel™ ELF, EF and LF release behaviour of milled extrudates with or without P-CO_2 injection as well as unprocessed physical mixtures. Plots of time vs. % drug release, which is the average of three replicates, were used as dissolution profiles for different formulations (Figure 6). These profiles demonstrated a significant improvement of KTP release in presence of P-CO_2 injection as compared to the other formulations. The release enhancement was observed as a direct result of the foam-like structure and high surface area of those extrudates with P-CO_2 injection[34–36].

Tablets evaluation

The bulk density and tap density of the tablet blends prepared with extrudates processed with P-CO_2 injection was lower as compared to the other blends without P-CO_2 injection and unprocessed physical mixtures, as a result of the foam extrudates (Table 6).

The evaluation of all KTP/Klucel™ ELF, EF and LF tablets showed that the drug content of all formulations ranged from 96–110% indicating good drug uniformity of all formulations. The tablet weight variations of all the formulations were acceptable with very low standard deviations (SD < 1.0). In case of the tablets prepared with foamed extrudates, tablet hardness was enhanced by 2.7–5.5 kp compared to those prepared by extrudates without P-CO_2 injection and unprocessed physical mixtures (Figure 7). Tablet friability was evaluated for all of the formulations and the results showed lowering in the % friability of tablets prepared with foamy extrudates (less than 0.3%) as compared to the other tablet formulations (0.6%–1.7%) (Figure 8). These results indicated good binding properties and compressibility of foamy extrudates.

The tablets were also subjected to *in vitro* dissolution studies of KTP/ Klucel™ EF tablets with and without P-CO_2 injection. The tablets used in the dissolution studies possessed the same hardness in order to avoid any discriminating effect of the disintegration on the release profiles. No significant differences were observed in the drug release profiles of tablets with and without P-CO_2 extrudates (Figure 9). These results indicate that the dissolution improvement of extrudates processed with P-CO_2 was due to the high surface area and porosity, as compared to the extrudates without P-CO_2 injection. Whereas, when these extrudates were compressed into tablets, the compression force reduced the surface area of the foamy extrudates which eliminates the dissolution improvements utilizing P-CO_2 injections. Therefore, there was no effect of P-CO_2 injection on the tablet release profile.

Conclusions

P-CO_2 acted as a temporary plasticizer for Klucel™ ELF, EF, LF when injected in zone 4 during HME processing, allowing reduction in extrusion temperatures. Whereas, when the P-CO_2 was injected in zone 6 the reduction in extrusion temperature was not feasible. Thus, the zone in which P-CO_2 is injected plays a significant role in melt extrusion processing. The microscopic morphology of the extrudates with P-CO_2 injection was changed to a foam-like structure, which increases their surface area and porosity. Moreover, the milling efficiency of all extrudates processed with P-CO_2 was enhanced, which may be beneficial for optimizing the manufacturing of solid dosage forms. A combination of P-CO_2 and HME

improved the tablet properties (higher hardness & lower friability) indicating good binding properties and compressibility of the blends. Furthermore, the extrudates processed with P-CO_2 injection demonstrated an enhancement of KTP release as compared to the physical mixtures and the extrudates processed without P-CO_2 injection, due to the increase in the surface area and porosity. Additionally, there was no significant difference in the drug release profiles of tablets prepared with or without CO_2 extrudates after the compression process, which indicates that P-CO_2 injection does not alter the drug release profiles of tablets. Alternatively, it instead improves the processing properties of the tablets. P-CO_2 utilized in HME processing may exhibit similar benefits of supercritical CO_2 however avoiding some of the disadvantages experienced when utilized at the supercritical level.

Acknowledgments

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References

1. Thakkar FMV, Soni T, Gohel M. Supercritical fluid technology: a promising approach to enhance the drug solubility. 2009; 1:1–14.
2. Vo CL-N, Park C, Lee B-J. Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics. 2013; 85:799–813. [PubMed: 24056053]
3. Chiou WL, Riegelman S. Preparation and dissolution characteristics of several fast release solid dispersions of griseofulvin. Journal of pharmaceutical sciences. 1969; 58:1505–1510. [PubMed: 5353269]
4. Gurunath S, Pradeep Kumar S, Basavaraj NK, Patil PA. Amorphous solid dispersion method for improving oral bioavailability of poorly water-soluble drugs. Journal of Pharmacy Research. 2013; 6:476–480.
5. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug discovery today. 2007; 12:1068–1075. [PubMed: 18061887]
6. Breitenbach J. Melt extrusion: from process to drug delivery technology. European Journal of Pharmaceutics and Biopharmaceutics. 2002; 54:107–117. [PubMed: 12191680]
7. Deng W, Majumdar S, Singh A, et al. Stabilization of fenofibrate in low molecular weight hydroxypropylcellulose matrices produced by hot-melt extrusion. Drug development and industrial pharmacy. 2013; 39:290–298. [PubMed: 22524504]
8. Chokshi RJ, Sandhu HK, Iyer RM, Shah NH, Malick AW, Zia H. Characterization of physico-mechanical properties of indomethacin and polymers to assess their suitability for hot-melt extrusion processs as a means to manufacture solid dispersion/solution. Journal of pharmaceutical sciences. 2005; 94:2463–2474. [PubMed: 16200544]
9. Terife G, Wang P, Faridi N, Gogos CG. Hot melt mixing and foaming of soluplus® and indomethacin. Polymer Engineering & Science. 2012; 52:1629–1639.
10. Repka MA, Battu SK, Upadhye SB, et al. Pharmaceutical applications of hot-melt extrusion: Part II. Drug development and industrial pharmacy. 2007; 33:1043–1057. [PubMed: 17963112]
11. He H, Yang R, Tang X. In vitro and in vivo evaluation of fenofibrate solid dispersion prepared by hot-melt extrusion. Drug development and industrial pharmacy. 2010; 36:681–687. [PubMed: 20136483]
12. Crowley MM, Zhang F, Repka MA, et al. Pharmaceutical applications of hot-melt extrusion: part I. Drug development and industrial pharmacy. 2007; 33:909–926. [PubMed: 17891577]
13. Arwidsson H, Hjelstuen O, Ingason D, Graffner C. Properties of ethyl cellulose films for extended release. II: Influence of plasticizer content and coalescence conditions when using aqueous dispersions. Acta pharmaceutica nordica. 1991; 3:65–70.

14. Elkovitch MD, Tomasko DL. Effect of supercritical carbon dioxide on morphology development during polymer blending. Polymer Engineering & Science. 2000; 40:1850–1861.
15. Medina-Gonzalez Y, Camy S, Condoret J-S. Cellulosic materials as biopolymers and supercritical CO_2 as a green process: chemistry and applications. International Journal of Sustainable Engineering. 2012; 5:47–65.
16. Subramaniam B, Rajewski RA, Snavely K. Pharmaceutical processing with supercritical carbon dioxide. Journal of pharmaceutical sciences. 1997; 86:885–890. [PubMed: 9269864]
17. Rizvi S, Mulvaney S, Sokhey A. The combined application of supercritical fluid and extrusion technology. Trends in Food Science & Technology. 1995; 6:232–240.
18. Kikic I, Vecchione F, Alessi P, Cortesi A, Eva F, Elvassore N. Polymer plasticization using supercritical carbon dioxide: experiment and modeling. Industrial & engineering chemistry research. 2003; 42:3022–3029.
19. Verreck G, Decorte A, Heymans K, et al. The effect of pressurized carbon dioxide as a temporary plasticizer and foaming agent on the hot stage extrusion process and extrudate properties of solid dispersions of itraconazole with PVP-VA 64. European journal of pharmaceutical sciences. 2005; 26:349–358. [PubMed: 16137869]
20. Verreck G, Decorte A, Heymans K, et al. Hot stage extrusion of p-amino salicylic acid with EC using CO2 as a temporary plasticizer. International journal of pharmaceutics. 2006; 327:45–50. [PubMed: 16930886]
21. Verreck G, Decorte A, Heymans K, et al. The effect of supercritical CO_2 as a reversible plasticizer and foaming agent on the hot stage extrusion of itraconazole with EC 20cps. The Journal of supercritical fluids. 2007; 40:153–162.
22. Verreck G, Decorte A, Li H, et al. The effect of pressurized carbon dioxide as a plasticizer and foaming agent on the hot melt extrusion process and extrudate properties of pharmaceutical polymers. The Journal of supercritical fluids. 2006; 38:383–391.
23. Lyons JG, Hallinan M, Kennedy JE, et al. Preparation of monolithic matrices for oral drug delivery using a supercritical fluid assisted hot melt extrusion process. International journal of pharmaceutics. 2007; 329:62–71. [PubMed: 17010544]
24. Sauceau M, Fages J, Common A, Nikitine C, Rodier E. New challenges in polymer foaming: a review of extrusion processes assisted by supercritical carbon dioxide. Progress in Polymer Science. 2011; 36:749–766.
25. Nalawade SP, Picchioni F, Janssen L. Supercritical carbon dioxide as a green solvent for processing polymer melts: Processing aspects and applications. Progress in Polymer Science. 2006; 31:19–43.
26. Ashland Specialty Ingredient, Klucel™ hydroxypropylcellulose physical and chemical properties. 2012:4.
27. Repka MA, Gerding TG, Repka SL, McGinity JW. Influence of plasticizers and drugs on the physical-mechanical properties of hydroxypropylcellulose films prepared by hot melt extrusion. Drug development and industrial pharmacy. 1999; 25:625–633. [PubMed: 10219532]
28. Vueba M, Batista de Carvalho L, Veiga F, Sousa J, Pina M. Influence of cellulose ether polymers on ketoprofen release from hydrophilic matrix tablets. European Journal of Pharmaceutics and Biopharmaceutics. 2004; 58:51–59. [PubMed: 15207537]
29. Tiţa D, Fuliaş A, Tiţa B. Thermal stability of ketoprofen—active substance and tablets. Journal of thermal analysis and calorimetry. 2011; 105:501–508.
30. Mohammed NN, Majumdar S, Singh A, et al. Klucel™ EF and ELF polymers for immediate-release oral dosage forms prepared by melt extrusion technology. AAPS PharmSciTech. 2012; 13:1158–1169. [PubMed: 22961411]
31. Crowley MM, Fredersdorf A, Schroeder B, et al. The influence of guaifenesin and ketoprofen on the properties of hot-melt extruded polyethylene oxide films. European Journal of Pharmaceutical Sciences. 2004; 22:409–418. [PubMed: 15265510]
32. http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm.).
33. Jeong H, Toledo R. Twin-screw extrusion at low temperature with carbon dioxide injection to assist expansion: extrudate characteristics. Journal of food engineering. 2004; 63:425–432.

34. Sprunk A, Page S, Kleinebudde P. Influence of process parameters and equipment on dry foam formulation properties using indomethacin as model drug. International journal of pharmaceutics. 2013; 455:189–196. [PubMed: 23891743]

35. Andrews GP, Abu-Diak O, Kusmanto F, Hornsby P, Hui Z, Jones DS. Physicochemical characterization and drug release properties of celecoxib hot melt extruded glass solutions. Journal of Pharmacy and Pharmacology. 2010; 62:1580–1590. [PubMed: 21072971]

36. Ahern RJ, Crean AM, Ryan KB. The influence of supercritical carbon dioxide (SC-CO_2) processing conditions on drug loading and physicochemical properties. International journal of pharmaceutics. 2012; 439:92–99. [PubMed: 23041132]

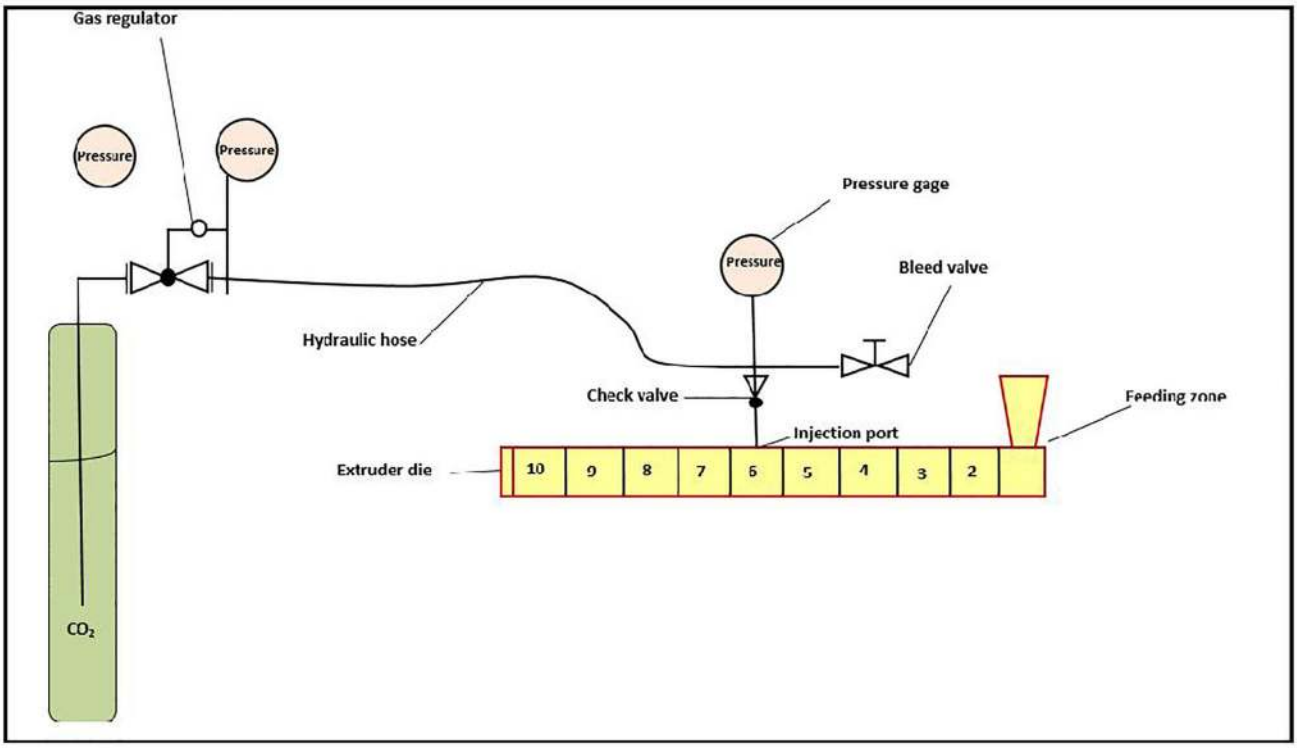

Figure 1.
Schematic diagram for P-CO_2 injection in hot melt extrusion processing.

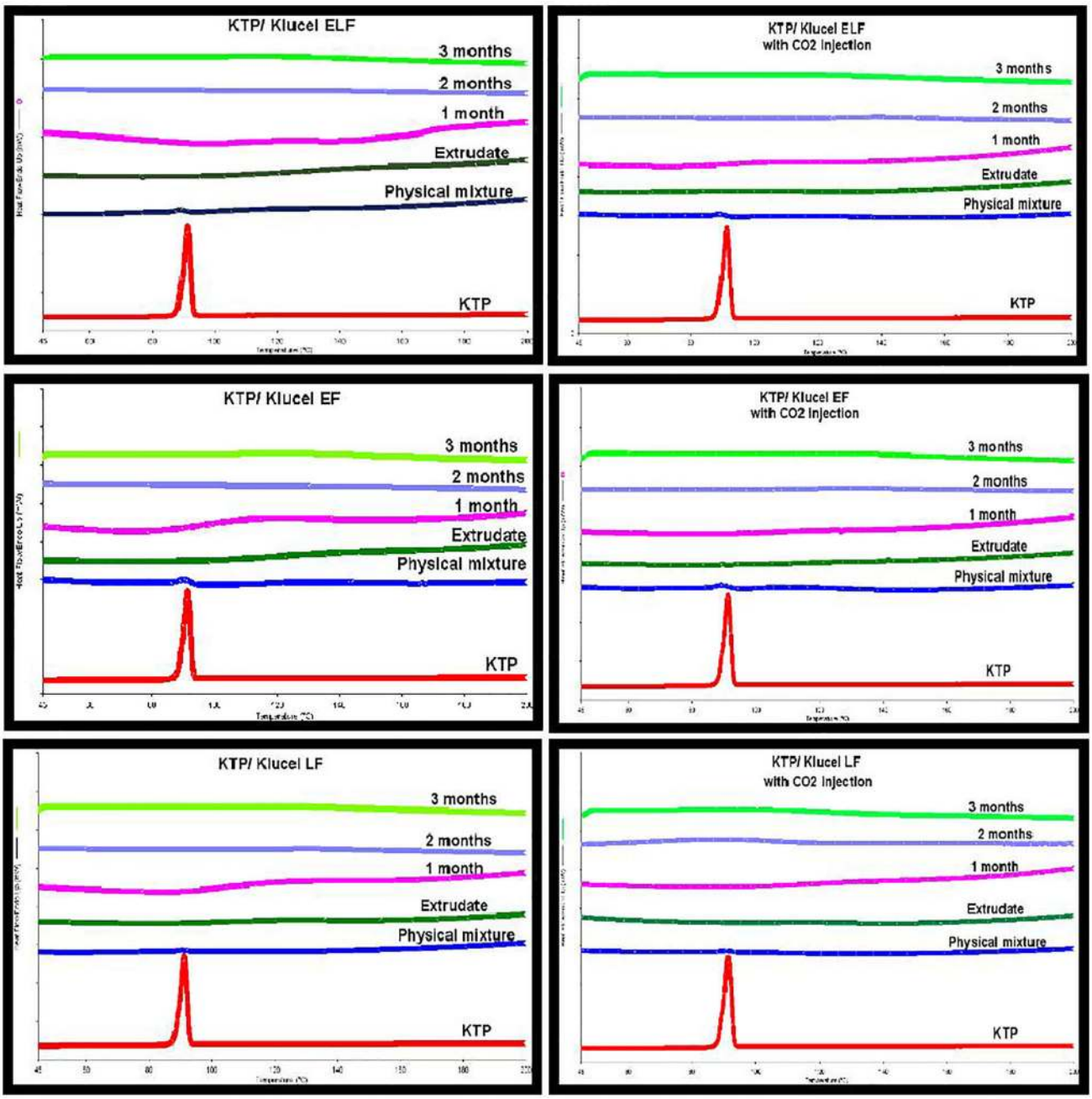

Figure 2.

DSC Thermogram of Ketoprofen, physical mixture and extrudates with and without P-CO_2 injection at 0, 1, 2, 3 months.

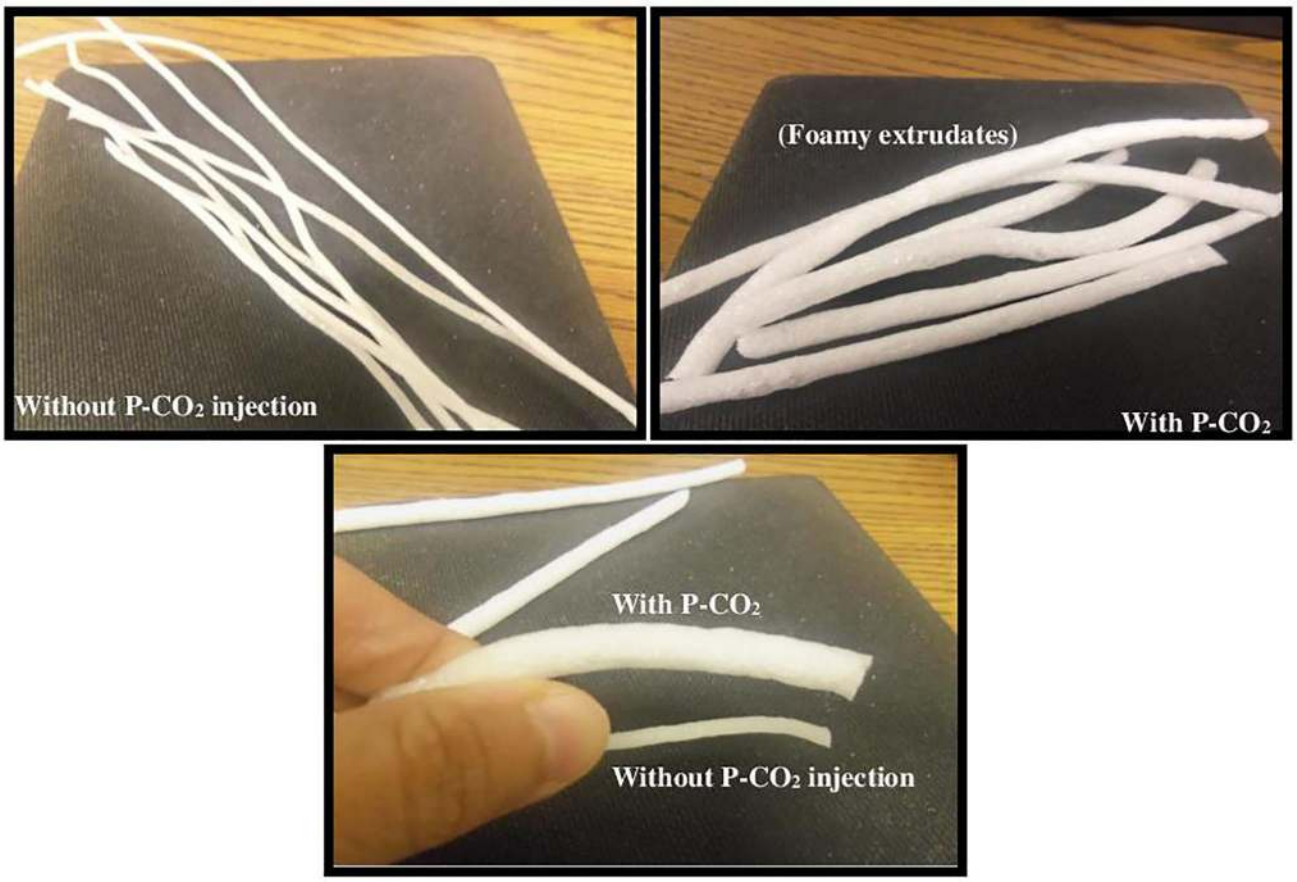

Figure 3.
HME extrudates processed with and without P-CO_2 injection.

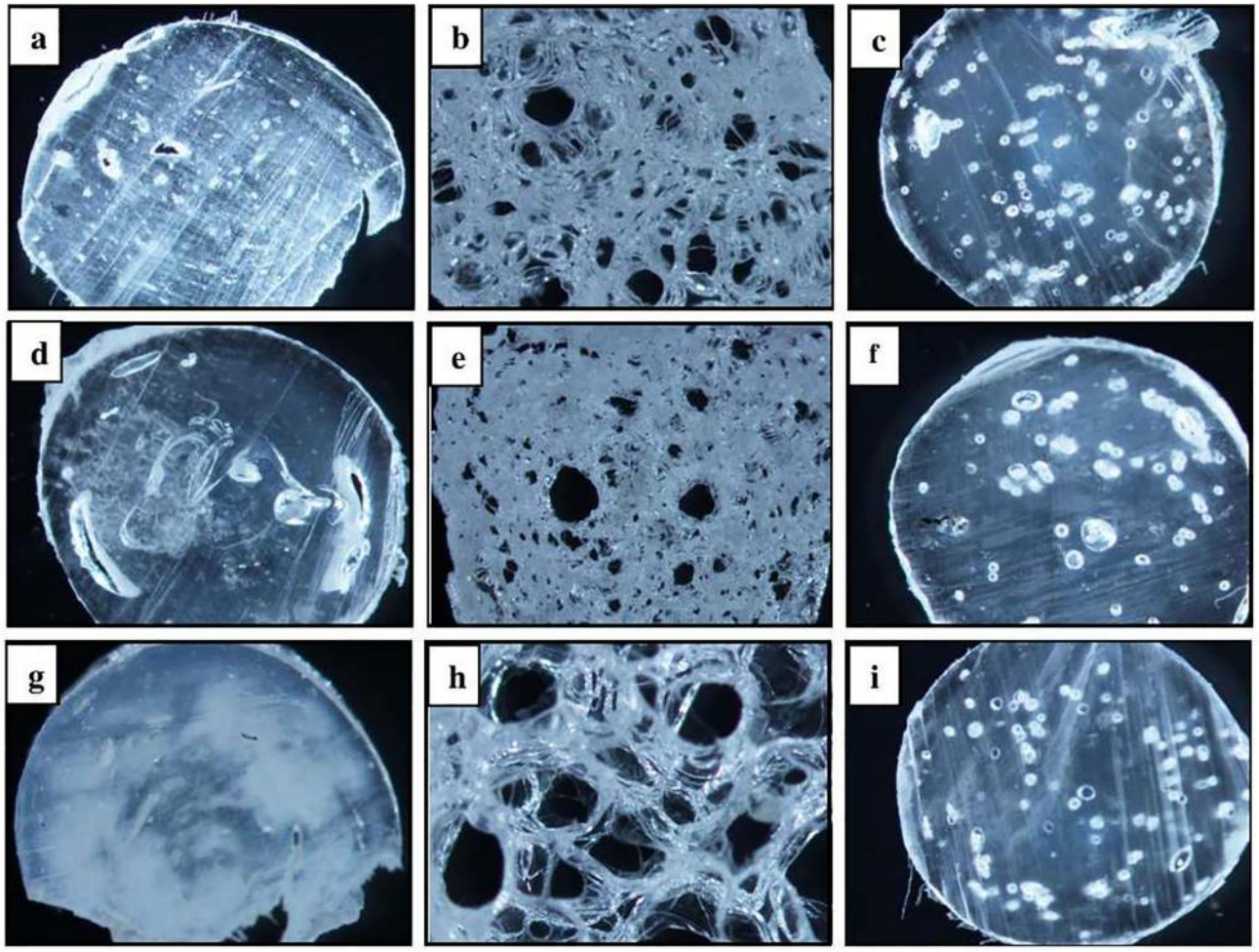

Figure 4.

Microscopy photographs of Klucel™ (ELF, EF, and LF) extrudates with and without P-CO_2 injection, or with PG injection (Magnification 3×). (a) ELF without P-CO_2, (b) ELF with P-CO_2, (c) ELF with PG injection, (d) EF without P-CO_2, (e) EF with P-CO_2, (f) EF with PG injection, (g) LF without P-CO_2, (h) LF with P-CO_2, (i) LF with PG injection.

Figure 5.
Failed milling of Klucel™ (ELF, EF, and LF) extrudates with PG injection.

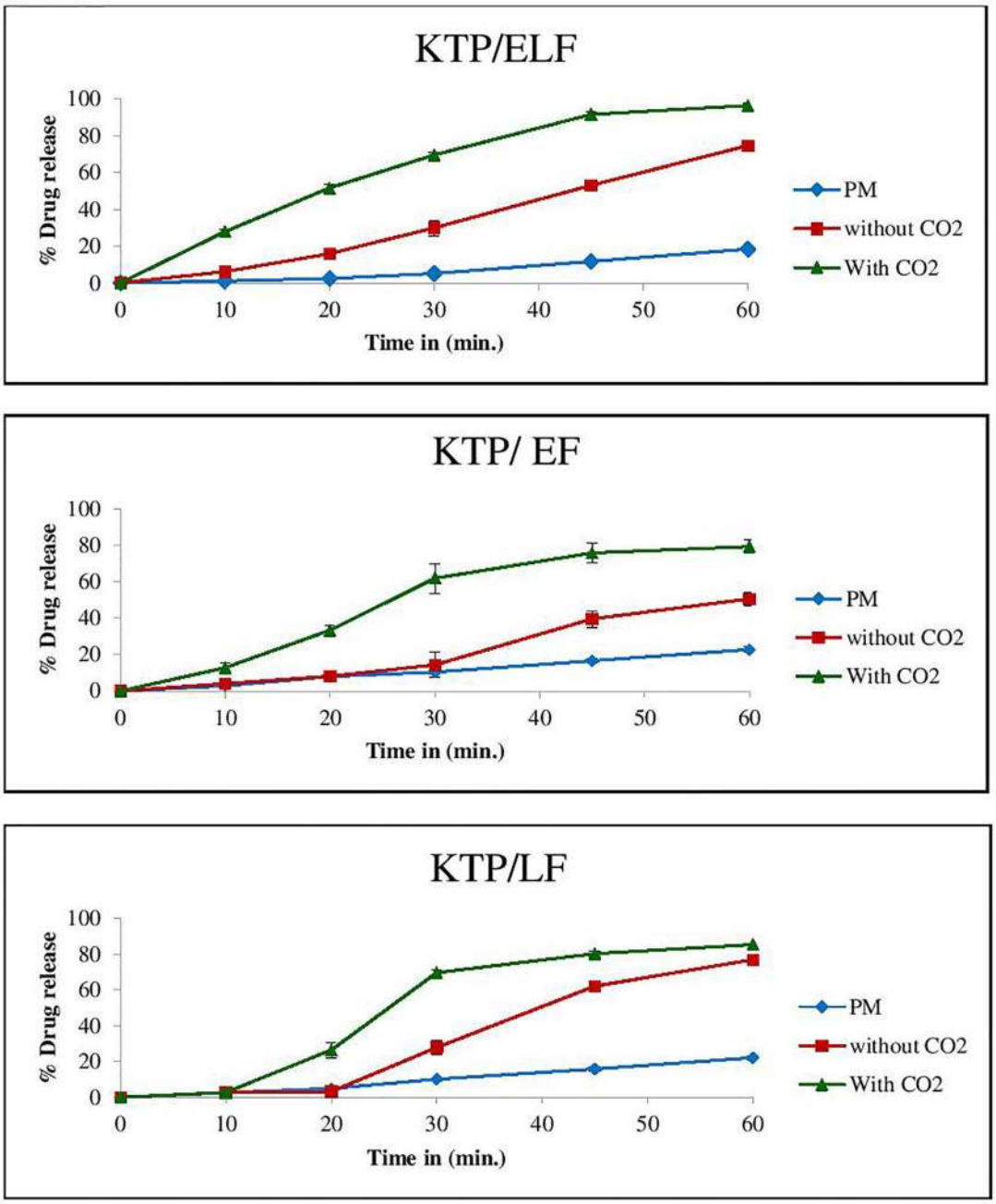

Figure 6.

Dissolution profiles of a. KTP/Klucel™ ELF, KTP/Klucel™ EF and KTP/Klucel™ LF extrudates with and without P-CO_2 injection and physical mixture. (pH 7.4 phosphate buffer, USP App II, 50 rpm/37°C).

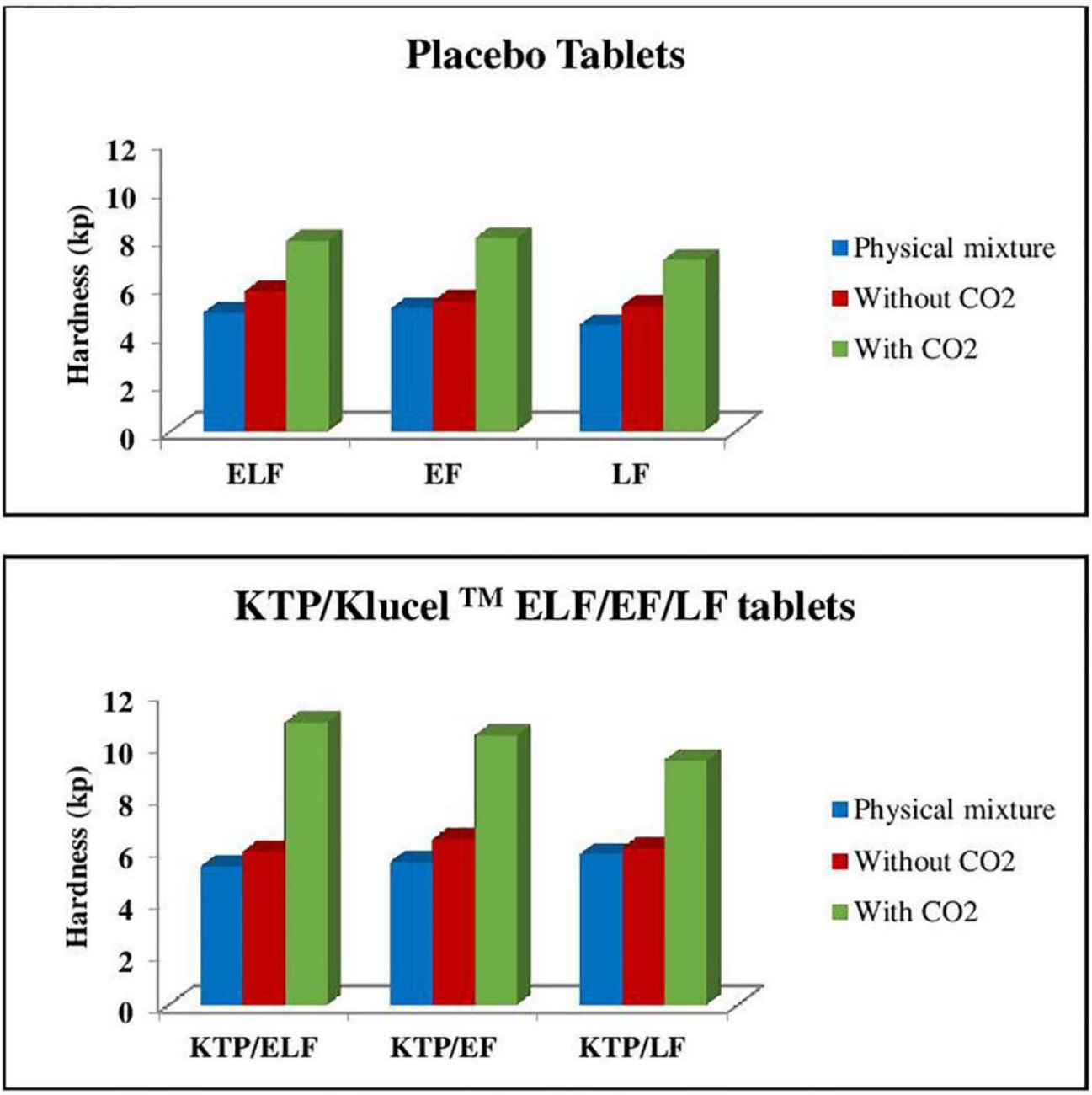

Figure 7.
Hardness in (kp) of Klucel™ ELF/EF/LF placebo tablets and KTP/Klucel™ ELF/EF/LF tablets, with and without P-CO2 injection and physical mixture.

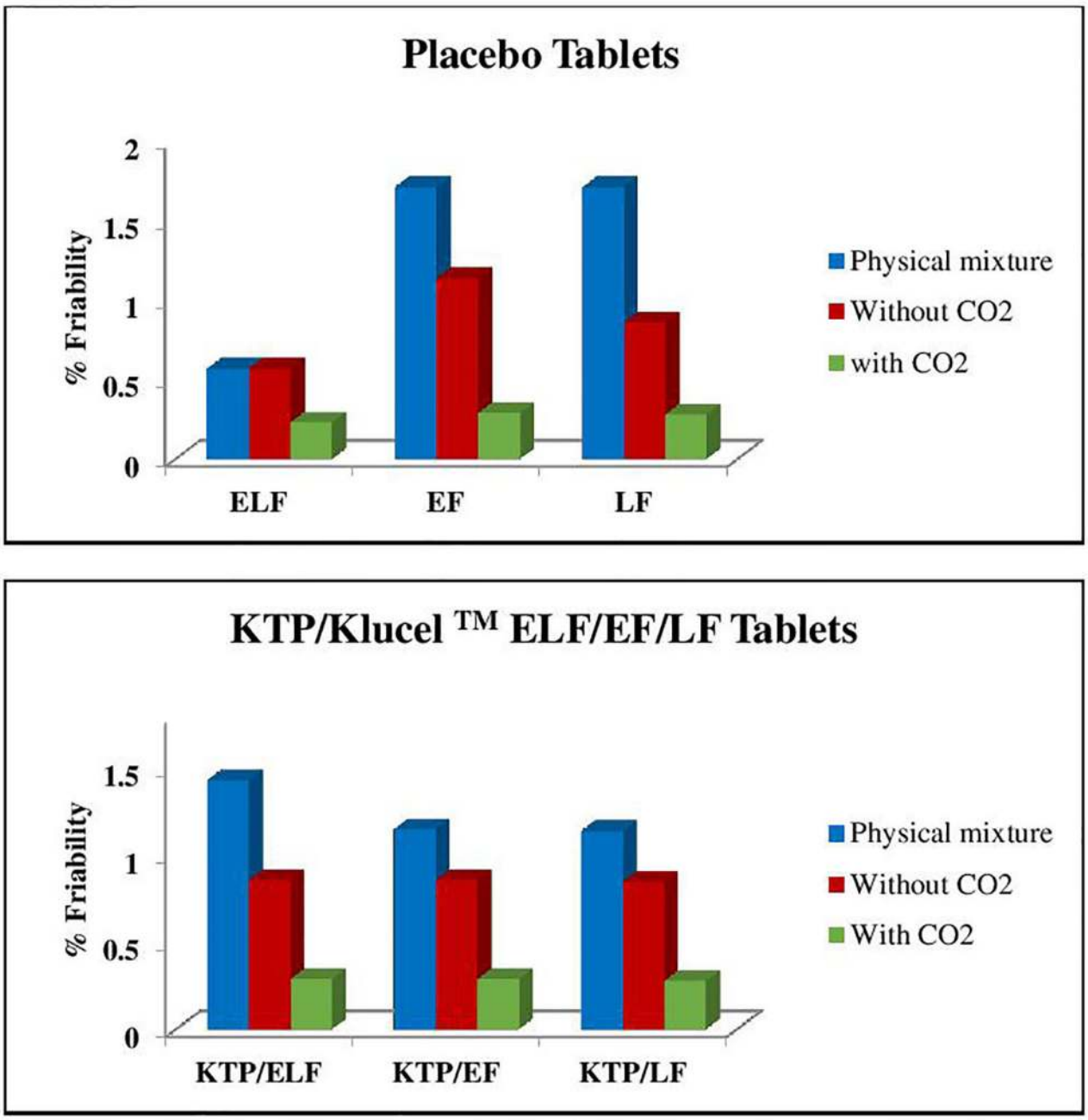

Figure 8.
% Friability of Klucel™ ELF/EF/LF placebo tablets and KTP/Klucel™ ELF/EF/LF tablets, with and without P-CO2 injection and physical mixture.

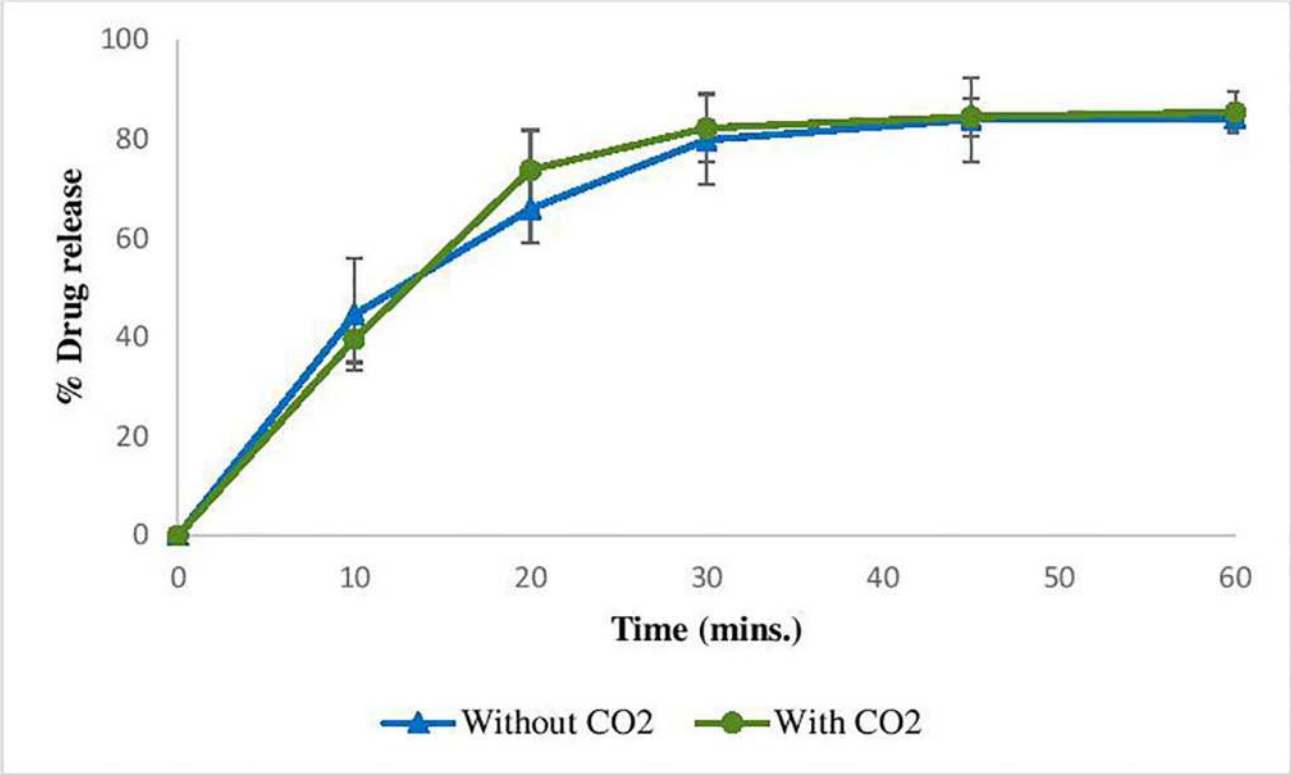

Figure 9.
Non-sink dissolution profiles of KTP/Klucel™ EF tablets with and without P-CO_2 injection and physical mixture. (Water, USP App II, 50 rpm and 37°C).

Table 1

Formulation composition of HME

Formulation	KTP (%)	Klucel™ ELF (%)	Klucel™ EF (%)	Klucel™ LF (%)	Propylene-glycol (PG) (%)	CO_2 injection zone
K_1	-	100	-	-	-	-
K_2	-	-	100	-	-	-
K_3	-	-	-	100	-	-
K_4	-	100	-	-	-	Zone 4
K_5	-	-	100	-	-	Zone 4
K_6	-	-	-	100	-	Zone 4
K_7	15	85	-	-	-	-
K_8	15	-	85	-	-	-
K_9	15	-	-	85	-	-
K_{10}	15	85	-	-	-	Zone 6
K_{11}	15	-	85	-	-	Zone 6
K_{12}	15	-	-	85	-	Zone 6
K_{13}	-	95	-	-	5	-
K_{14}	-	-	95	-	5	-
K_{15}	-	-	-	95	5	-

Table 2

Placebo tablet composition for non-API extrudates with and without P-CO_2 injection and physical mixture of non-extruded polymers.

Excipients	% (w/w)	Weight (mg/tablet)
Klucel™ (ELF/EF/LF)	28.57	50.00
Avicel® 102	68.00	119.00
Aerosil®	0.57	1.00
Polyplasdone™ XL	2.29	4.00
Magnesium stearate	0.57	1.00

Table 3

KTP tablet composition of extrudates with and without P-CO_2 injection.

Excipients	%(w/w)	Weight (mg/tablet)
KTP	7.14	25.00
Klucel™ (ELF/EF/LF)	40.46	141.66
Avicel® 102	24.60	86.10
Flowlac 90	12.30	43.05
Syloid®	10.00	35.00
Polyplasdone™ XL	5.00	17.5
Magnesium stearate	0.50	1.75

Table 4

Processing parameters for hot melt extrusion process of K_1-K_{15}

Formula	Extrusion Temp. (°C)	Screw Speed (rpm)	Torque (Nm)
K_1	140	100	21–22
K_2	140	100	22
K_3	140	100	20–22
K_4	Zone 2–4 (140 °C)	100	18–18.5
	Rest of the zones (120 °C)		
K_5	Zone 2–4 (140 °C)	100	18
	Rest of the zones (120 °C)		
K_6	Zone 2–4 (140 °C)	100	17–19
	Rest of the zones (120°C)		
K_7	110	75	9–14
K_8	110	75	9–12
K_9	110	75	11–13
K_{10}	100	75	8–9
K_{11}	100	75	9–10
K_{12}	100	75	9–12
K_{13}	90	100	12–16
K_{14}	90	100	12–17
K_{15}	90	100	14–18

Table 5

Bulk and tap density of milled extrudates with and without P-CO_2 injection (g/ml)

Sample name	Without P-CO_2 injection		With P-CO_2 injection	
	Bulk density	Tap density	Bulk density	Tap density
Klucel™ ELF	0.265	0.366	0.154	0.241
Klucel™ EF	0.294	0.441	0.131	0.213
Klucel™ LF	0.304	0.435	0.191	0.227
KTP/ Klucel™ ELF	0.382	0.434	0.175	0.270
KTP/ Klucel™ EF	0.286	0.373	0.150	0.235
KTP/ Klucel™ LF	0.325	0.415	0.145	0.240

Table 6

Bulk and Tap density of placebo and KTP tablet blends (g/ml)

Sample name	Physical mixture		Without P-CO_2 injection		With P-CO_2 injection	
	Bulk density	Tap density	Bulk density	Tap density	Bulk density	Tap density
Klucel™ ELF	0.393	0.492	0.366	0.473	0.303	0.419
Klucel™ EF	0.395	0.51	0.385	0.485	0.303	0.413
Klucel™ LF	0.407	0.516	0.393	0.492	0.354	0.462
KTP/ Klucel™ ELF	0.40	0.61	0.46	0.66	0.35	0.49
KTP/ Klucel™ EF	0.39	0.57	0.44	0.59	0.33	0.47
KTP/ Klucel™ LF	0.39	0.57	0.44	0.59	0.33	0.47

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