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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-CO₂) 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-CO₂ on the various polymers tested.

Methods—The physico-mechanical properties of extrudates with and without injection of P-CO₂ 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-CO₂ were evaluated.

Results & conclusion—P-CO₂ 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 CO₂ at the extrusion die. The foamy extrudates demonstrated enhanced KTP release compared to the extrudates processed without P-CO₂ 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-CO₂ 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-CO₂); Ketoprofen (KTP); Hydroxypropylcellulose (HPC); Foamy extrudates

Introduction

Solubility is considered 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 bioavailability². 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 solubility 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 techniques¹. 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 dispersions⁶. 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 state⁹. 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 thermolabile drugs, processing aids or plasticizers might be added to reduce the viscosity and lower the minimum processing temperature, thus decreasing both drug and polymer degradation¹². Choice of plasticizers 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 extrudates¹². Some plasticizers adversely affect the storage stability of pharmaceutical formulations resulting in changes within their release profiles¹³.

It has been reported that P-CO₂ can act as a reversible plasticizer and foaming agent¹⁴. CO₂ is non-toxic, non flammable and chemically inert in nature^{15, 16}. These properties could increase the interest of the combination of P-CO₂ and HME¹⁷. Previous investigation have shown that P-CO₂ 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-CO₂ 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 CO₂ on HME processing. However, limited studies have been conducted to study the effect of the pressurized (*subcritical*) state of CO₂. P- CO₂ entails more advantages than supercritical CO₂ 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, thickener and drug carrier²⁶. Typically, HPC extrudates may be difficult to mill due to its high elasticity and hygroscopicity²⁷. 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-CO₂ 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 form²⁸. It is thermally stable with a melting point of approximately 95°C and “burns out” over a temperature range of 235–400°C²⁹. Indeed the literature has recently reported that hot melt extrudates of KTP and HPC has demonstrated poor milling efficiency³⁰. In order to solve these underlining issues, in the present study we investigated the effect of P-CO₂ 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). CO₂ 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). Approximately 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 conveying 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. CO₂ 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 CO₂ was regulated using the regulator knob.

Light Microscopy

To evaluate the microscopic morphology of the extrudates with and without P-CO₂ 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 equipped 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 detector wavelength for KTP detection was set at 256 nm.

Tableting

The milled extrudates were used to prepare the tablet blends using microcrystalline 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.

$$F = \frac{W_1 - W_2}{W_1} \times 100$$

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-CO₂ injection were sealed in glass bottles and stored at 25°C/60% RH for three months. Recrystallization 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-CO₂ 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-CO₂ injection, metering of CO₂ was controlled using the regulator until the reading on the pressure guage located at the 4-way connector was maintained between 75–150 psi. CO₂ was provided in a liquid form from a CO₂ gas cylinder (pure

clean). The back pressure from the injection port maintained the CO₂ 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 CO₂. As described by Verreck *et al.*, 2007d, diffusion and dissolution of the injected P-CO₂ in the polymers manifested as extremely foamy extrudates with the increment of die swelling accompanied by CO₂ expansion at the terminal end of the die (Figure 3). As investigated by Repka *et al.*, HPC extrudates were more dense, flexible and hygroscopic²⁷. 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-CO₂ can also act as a plasticizer which has been previously mentioned by Lyons *et al.*²³. In formulations of k₄, k₅ and k₆ when P-CO₂ was injected in zone 4, the processing temperature decreased by about 20°C as compared to the processing temperature without injecting P-CO₂ (Table 4). These findings confirmed that CO₂ 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, CO₂ is chemically inert, so the compatibility issue of other plasticizers with the polymers and APIs used in the study, was avoided. Plasticization effect of CO₂ was not feasible when P-CO₂ was injected in zone 6 (formulation k₁₀, k₁₁, and k₁₂) due to the short distance between zone 6 and the extruder die.

The microscopical images of the extrudates processed with P-CO₂ injection demonstrated higher surface area and porosity as compared to the extrudates processed without P-CO₂ 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 procedure³⁰. 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-CO₂ 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-CO₂ injection³³. Our results showed that foamed milled extrudates exhibited lower bulk density and tap density as compared to the extrudates without P-CO₂ 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-CO₂ 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-CO₂ 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-CO₂ injection^{34–36}.

Tablets evaluation

The bulk density and tap density of the tablet blends prepared with extrudates processed with P-CO₂ injection was lower as compared to the other blends without P-CO₂ 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-CO₂ 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-CO₂ 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-CO₂ extrudates (Figure 9). These results indicate that the dissolution improvement of extrudates processed with P-CO₂ was due to the high surface area and porosity, as compared to the extrudates without P-CO₂ 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-CO₂ injections. Therefore, there was no effect of P-CO₂ injection on the tablet release profile.

Conclusions

P-CO₂ 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-CO₂ was injected in zone 6 the reduction in extrusion temperature was not feasible. Thus, the zone in which P-CO₂ is injected plays a significant role in melt extrusion processing. The microscopic morphology of the extrudates with P-CO₂ 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-CO₂ was enhanced, which may be beneficial for optimizing the manufacturing of solid dosage forms. A combination of P-CO₂ 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-CO₂ injection demonstrated an enhancement of KTP release as compared to the physical mixtures and the extrudates processed without P-CO₂ 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 CO₂ extrudates after the compression process, which indicates that P-CO₂ injection does not alter the drug release profiles of tablets. Alternatively, it instead improves the processing properties of the tablets. P-CO₂ utilized in HME processing may exhibit similar benefits of supercritical CO₂ however avoiding some of the disadvantages experienced when utilized at the supercritical level.

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Figure 1.
Schematic diagram for P-CO₂ injection in hot melt extrusion processing.

Figure 2.
DSC Thermogram of Ketoprofen, physical mixture and extrudates with and without P-CO₂ injection at 0, 1, 2, 3 months.

Figure 3.
HME extrudates processed with and without P-CO₂ injection.

Figure 4. Microscopy photographs of Klucel™ (ELF, EF, and LF) extrudates with and without P-CO₂ injection, or with PG injection (Magnification 3×). (a) ELF without P-CO₂, (b) ELF with P-CO₂, (c) ELF with PG injection, (d) EF without P-CO₂, (e) EF with P-CO₂, (f) EF with PG injection, (g) LF without P-CO₂, (h) LF with P-CO₂, (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-CO₂ 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-CO₂ 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-CO₂ 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
Polypladone™ XL	2.29	4.00
Magnesium stearate	0.57	1.00

Table 3KTP tablet composition of extrudates with and without P-CO₂ 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 4Processing parameters for hot melt extrusion process of K₁-K₁₅

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 5Bulk and tap density of milled extrudates with and without P-CO₂ 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