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Formulation and evaluation of new oxycodone extended release multiple unit pellet system

Original Paper

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Abstract The goal of the present study is to prepare a stable, multiple-unit, extended-release dosage form containing oxycodone pellets coated with aqueous ethylcellulose (EC) dispersion, Surelease E-7-19050. The application of 18% w/w of EC leads to the similar drug release with the hydrophobic, non-swelling, matrix reference product containing 20 mg of oxycodone. Increasing the compression force to 9 kN and including more than 50% w/w of oxycodone pellets into the formulation resulted in faster drug release, indicating the damaging to the EC film coating. The physical appearance of the final formulation, assay of oxycodone, moisture content, and dissolution data over the stability period showed that the multiple-unit pellet system (MUPS) is efficient for the production of highly stable product.

Keywords *Opioids – Oxycodone - Dissolution – Extended release - Pellets*

INTRODUCTION

Coated pellets are frequently used for oral, controlled-release, drug delivery. The recent trends indicate that multiparticulate drug delivery systems are especially suitable for achieving controlled- or delayed-release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns, as well as reproducible and short gastric residence time (Dey et al., 2008). Controlled-release drug delivery systems provide a uniform concentration at absorption site, maintain plasma concentration within a therapeutic range, reduce the frequency of administration, and minimizes the side effects. It is also important to avoid dose dumping after the oral administration of ER dosage forms, especially for drugs that possess the characteristics of a higher solubility, higher dose, or a fatal side effect (Uros et al., 2014). Furthermore, an alcohol-induced dose dumping effect in oral ER dosage forms has gained increased attention in the recent years (Jedinger et al., 2014).

Compaction of multiparticulates, commonly called MUPS (abbreviation for multiple-unit pellet system), is one of the most recent and challenging technologies that combine the advantages of both tablets and pellet-filled capsules in one dosage form. The multiparticulates spread uniformly throughout the gastrointestinal tract, resulting in less variable bioavailability and a reduced risk of local irritation. Various drug release profiles can be obtained by simply mixing pellets with different release characteristics or incompatible drugs can be easily separated (Dashevsky et al., 2004).

Oxycodone hydrochloride is a semisynthetic opioid agonist that provides effective relief for moderate to severe pain in cancer and postoperative patients. The pharmacokinetic and steady-state pharmacodynamic studies with immediate-release (IR) oxycodone have shown it to be well tolerated, with adverse effects similar to those of other opioids. The bioavailability of oral oxycodone in humans is 60% (range: 50–87%). The terminal elimination half-life is independent of dose, with modest interindividual differences (Fukui et al., 2017).

Ethylcellulose (EC) has been widely used as a barrier membrane or binder to prepare pharmaceutical, oral,

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Table 1. Formulation of oxycodone MUPS tablets F1–F3 (weights in mg/tablet)

Process step	Material	Formulation code		
		F1	F2	F3
Oxycodone drug layered pellets	Oxycodone hydrochloride	20.0	20.0	20.0
	Hypromellose (Methocel E5)	1.2	1.2	1.2
	Polysorbate 80	1.2	1.2	1.2
	Talc	0.5	0.5	0.5
	Sugar spheres with a diameter of 355–425 µm	50.0	50.0	50.0
Release modifying polymer	Surelease clear E-7-19050*	11.7* (7.3 mg EC)	21.0* (13.1 mg EC)	30.4* (19.0 mg EC)
Compression into MUPS	Microcrystalline cellulose (Comprecel M102)	124.1	137.5	150.8
	Magnesium stearate	2.2	2.4	2.6
	Silica dioxide	1.1	1.2	1.3
MUPS tablet weight in mg		**212.0**	**235.0**	**258.0**

** Surelease clear E-7-19050 contains 62.4% w/w of EC.*
EC, ethylcellulose.

modified-release dosage forms. The aqueous dispersion of EC, for example, Surelease, has been used to manufacture modified-release multiparticulates for filling into capsules and single-unit tablets or soft-gel capsules through film-coating applications. In addition, the use of aqueous EC dispersion as a release retardant binder for the manufacture of inert matrices has been reported. Surelease® enhanced the compaction characteristics of the drug, and the drug was released from those inert porous matrices by diffusion (Rajabi-Siahboomi & Farrell, 2008).

MATERIALS AND METHODS

Materials

The materials used in this study were oxycodone hydrochloride (Saneca Pharmaceuticals, Slovakia), sugar spheres with a diameter of 355–425 µm (Hanns G. Werner, Germany), talc (Luzenac, China), hypromellose (HPMC, Methocel E5, Dow Chemicals, GB), polysorbate 80 (Centralchem, Slovakia), Surelease clear E-7-19050 (Colorcon, USA), microcrystalline cellulose (Comprecel M102, Mingtai, China), silica dioxide (Grace GmbH, GB), and magnesium stearate (Faci SPA, Italia).

METHODS

Preparation of opiate pellets

The spraying of water dispersion method was chosen to prepare the opioid analgesic pellets. The required quantities of hypromellose and polysorbate 80 were dispersed in water, purified to prepare binding suspension, and mixed until clear solution is achieved. Oxycodone HCl powder was then added to the dispersion and mixed for another 45 min. The required quantity of Talc was added at the end of oxycodone dispersion preparation and mixed for 20 min. Required amount of sugar spheres with a diameter of 355–425 µm was loaded into a fluidized bed coater Glatt GPCG-2 equipped with a 3.0-L Wurster container, air distribution plate type A, and filter bags with a porosity of below 20 µm (Glatt GmbH, Germany) and preheated to a product temperature of 34–36°C. The layering conditions were given as follows: batch size, 400 g; inlet air temperature, 45°C; product temperature, 33°C; air flow, 120 m^3/h; nozzle diameter, 1.2 mm; atomizing air pressure, 1.5 bar; spray rate, 5 g/min; final drying at 40°C for 20 min.

Coating of drug-layered pellets

The oxycodone drug-layered pellets were coated with aqueous water dispersion of Surelease E-7-19050 (15% w/w solid content) using the fluidized bed coater Glatt GPCG-2 (Glatt GmbH, Germany) and preheated to a product temperature of 36–48°C. Three different quantities of Surelease E-7-19050 were applied onto oxycodone pellets (formulations F1–F3, Table 1). The layering conditions were given as follows: batch size, 400 g; inlet air temperature, 50°C; product temperature, 35°C; air flow, 140 m^3/h; nozzle diameter, 1.2 mm; atomizing air pressure, 1.5 bar; spray rate, 8 g/min; final drying at 45°C for 30 min.

Compression of coated pellets

The composition of MUPS tablets F1–F3 is presented in Table 1. Coated pellets were mixed in a slow speed blender RV1 (Kovymont, Slovakia) for 15 min at 13 rpm with different amounts of microcrystalline cellulose (Comprecel M102).

Table 2. Formulation of oxycodone MUPS tablets F4–F6 (weights in mg/tablet)

Process step	Material	Formulation code		
		F4	F5	F6
Oxycodone drug layered pellets	Oxycodone hydrochloride	20.0	20.0	20.0
	Hypromellose (Methocel E5)	1.2	1.2	1.2
	Polysorbate 80	1.2	1.2	1.2
	Talc	0.5	0.5	0.5
	Sugar spheres with a diameter of 355–425 µm	50.0	50.0	50.0
Release modifying polymer	Surelease clear E-7-19050*	21.0* (13.1 mg EC)	21.0* (13.1 mg EC)	21.0* (13.1 mg EC)
Compression into MUPS	Microcrystalline cellulose (Comprecel M102)	214.4	91.3	38.1
	Magnesium stearate	3.1	1.9	1.3
	Silica dioxide	1.6	0.9	0.7
MUPS tablet weight in mg		**313.0**	**188.0**	**134.0**

** Surelease clear E-7-19050 contains 62.4% w/w of EC.*
EC, ethylcellulose.

After that 1.0% of magnesium stearate and 0.5% of silica dioxide were added as a lubricant/glidant (Table 2) and mixed in the slow speed blender RV1 for 5 min at 13 rpm. The tablets were compressed on a rotary tablet press Pressima AX8 (IMA Pharma, Italy) with different compression forces; the composition and tablet weight of formulations F1–F6 are presented in Tables 1 and 2. The hardness of tablets was tested using a hardness tester Sotax Tester 8M (Sotax AG, Switzerland), and the disintegration of 6 MUPS tablets in water (temperature 35–39°C) was performed using a disintegration tester Sotax DT2 (Sotax AG, Switzerland). The friability of 6.5g of MUPS tablets was tested using a Sotax friability tester (Sotax AG, Switzerland) and evaluated after 100 rotations of the drum. The physical characteristics of MUPS fromulations F1–F6 are reported in Table 3.

In vitro dissolution study

The drug release from the coated and compressed pellets was investigated using a paddle apparatus Sotax AT7 Smart (Sotax AG, Switzerland) in 900 mL of 0.1N HCl at 75 rpm at 37 ± 0.5°C, $n = 6$. Samples were withdrawn at predetermined time points (sample volume: 1.5 mL) and measured using UV spectrophotometer (Cary 50 UV-VIS spectrophotometer, Agilent technologies) at 230 nm.

Tablets bulk stability testing

The final formulation of oxycodone MUPS tablets was set for stability study in double PE bags with a dessicant placed between them and closed in a nontransparent plastic container for 3 months at a relative temperature (RT) and relative humidity (RH) conditions in 3 different stability chambers SC-12 Plus (REMI Laboratory Instruments, India): 25°C/60%, 30°C/65%, and 40°C/75%. After each month, dissolution, appearance, assay, and LOD (halogen analyser Mettler Toledo HF63, 10 min at 105°C, 5-g samples of crushed tablets) were performed and evaluated.

RESULTS AND DISCUSSION

Compaction of multiparticulates, commonly called MUPS, is one of the most recent and challenging technologies that combine the advantages of both tablets and pellet-filled capsules in one dosage form. Ideally, the compacted pellets should not fuse into a nondisintegrating matrix during compression and should disintegrate rapidly into individual pellets in gastrointestinal fluids. Importantly, the drug release should not be affected by the compaction process and the polymer coating must be able to resist to the compression force; it can deform, but it should not rupture (Bhad et al., 2010). Most studies on the compression of pellets with EC revealed damage to the coating layer with a loss of the extended-release properties. The mechanical properties of the particular Surelease E-7-19050 polymer coating were determined in order to investigate its suitability for the coating of oxycodone pellets, which are intended to be compressed into tablets.

Figure 1 shows drug release profiles of MUPS compressed using oxycodone coated pellets with different concentration of retarding agent Surelease E-7-19050: 10% w/w (referring to the active oxycodone pellets, see composition in Table 1) of EC (EC, Formulation F1), 18% w/w of EC (F2), and 26% w/w of EC (F3). The formulations F1–F3 were compressed at the same main compression force of 4.5 kN. The dissolution profiles are compared with the commercially available reference

Table 3. Physical characteristics of oxycodone MUPS tablets F1–F6

Formulation code	Average weight [mg], *n = 20*	Hardness [N], *n = 10*	Friability [25 rpm, 4 min, %], *n = 3*	Disintegration [s], *n = 6*
F1	212.2 ± 2.9	51 ± 5.4	0.51 ± 0.08	31 ± 5.8
F2	235.2 ± 2.7	52 ± 6.3	0.47 ± 0.10	24 ± 7.5
F3	258.8 ± 3.6	54 ± 5.8	0.56 ± 0.06	42 ± 4.2
F4	313.0 ± 2.4	76 ± 5.0	0.50 ± 0.07	35 ± 2.8
F5	188.6 ± 2.2	41 ± 4.2	0.35 ± 0.06	161 ± 12.1
F6	134.7 ± 2.9	43 ± 3.6	0.28 ± 0.04	987 ± 9.9
F4 (3 kN)	313.6 ± 3.8	38 ± 4.1	0.91 ± 0.06	24 ± 1.8
F4 (6 kN)	314.2 ± 2.1	54 ± 3.0	0.65 ± 0.02	124 ± 8.2
F4 (9 kN)	313.4 ± 1.2	78 ± 2.6	0.04 ± 0.01	997 ± 13.4

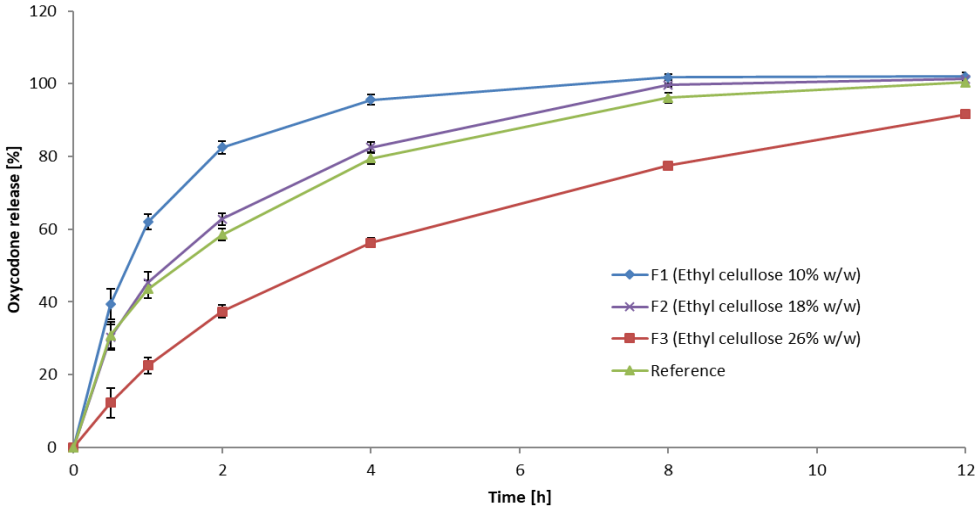

Figure 1. Influence of Ethyl celullose content on oxycodone drug release from MUPS tablets F1-F3

product, Targin® (Mundipharma, Austria), containing 20 mg of oxycodone hydrochloride in a hydrophobic, non-swellable matrix tablets. As it can be seen, the release decreased with increasing EC content and the similar dissolution profile (similarity factor *f2 = 84*) was achieved with formulation F2 containing 18% w/w of EC (Surelease E-7-19050). Following this observation, the effect of filler/pellet content was further investigated with this concentration of EC.

Three formulations, F4, F5, and F6 (containing 18% w/w of EC, see composition in Table 2), were prepared with different oxycodone pellet content, 30%, 50% and 70% w/w, mixed with extragranular excipients and compressed at the same main compression force of 4.5 kN. The oxycodone release from compressed pellets was significantly faster compared with that from the original pellets coated with 18% of EC as shown in Figure 2. This could be explained by the weak mechanical properties of EC films, which ruptured during compression. It has been reported that plastically deforming excipients are more effective in protecting the coated pellets during compression; therefore, the microcrystalline cellulose (Comprecel M102) was selected to provide a better protective effect to the oxycodone-coated pellets. Figure 2 shows that increasing the protective excipient to 70% w/w (30% pellet content, formulation F4) minimized the damage to the compressed drug pellets, with the *f2* between compressed and uncompressed pellets being 61. Values for *f2* (similarity factor) between 50 and 100 indicate that the two profiles are similar (Vetchý et al., 2014). Compressing coated pellets with 30% of protective excipient (formulation F6) resulted in the loss of their extended-release properties. This is explained by the lower yield pressure of the MCC filler that absorbs the energy of compaction and preferentially deforms under pressure, thus protecting the pellets. A higher level of the cushioning excipient also reduces the number of oxycodone

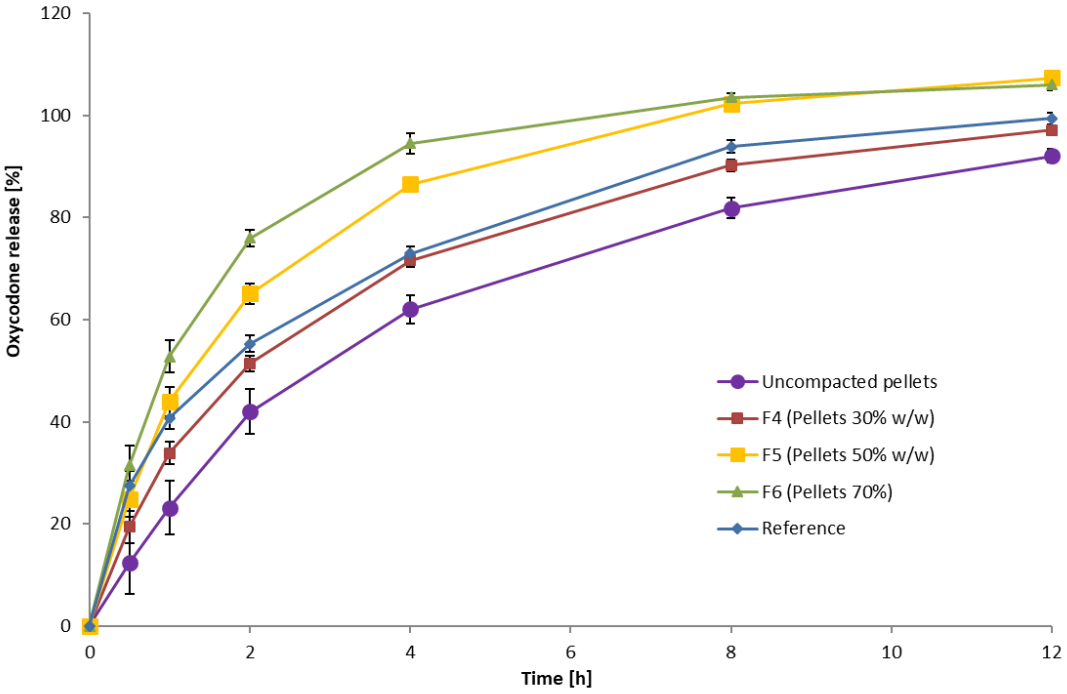

Figure 2. Influence of proportion of coated pellets on oxycodone drug release from MUPS tablets F4-F6

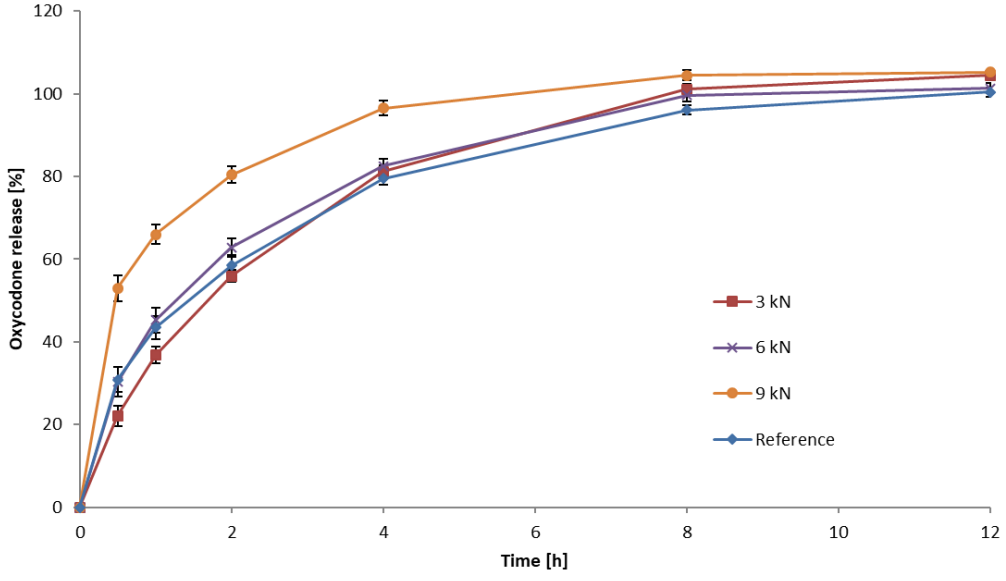

Figure 3. Influence of compression force on oxycodone drug release from MUPS tablets containing 30% w/w proportion of coated pellets

pellets coming in direct contact with each other or with the punch surface during the compression cycle, which can cause pellets to rupture (Al-Hashimi et al., 2018).

Figure 3 shows drug release profile of MUPS compressed at different compression forces using 30% w/w oxycodone pellets content in the formulation. Increasing compression force resulted in faster drug release, indicating the damaging to the EC film coating. The *f2* values for tablets compressed at a compression force of 3 and 6 kN were 71 and 62, respectively, compared with the matrix reference tablets, Targin. Increasing the tablet compression force to 9 kN leads to MUPS tablets of greater strength; however, an increase in tablet disintegration time to more than 15 min was also observed (Table 3). Higher disintegration time could be attributed to a lower penetration of the disintegration test media into the tablet because of the creation of undesirable matrix structure.

Table 4. Stability data of oxycodone MUPS tablets at different time intervals in three different conditions (formulation F4)*

Parameters	Initial	25°C/60% RH			30°C/65% RH			40°C/75% RH		
		1M	2M	3M	1M	2M	3M	1M	2M	3M
Assay %	98.7	98.4	98.0	97.7	98.2	98.4	98.0	97.4	97.0	97.2
Appearance (white to off-white, round, biconvex tablets)	Comply	Comply	Comply	Comply	Comply	Comply	Comply	Comply	Comply	Slightly yellowish
Loss on drying %	2.8	3.5	3.8	3.8	3.8	3.8	3.9	4.0	4.2	4.4
Q8	85.91	84.24	84.65	82.17	82.01	82.53	79.85	83.08	81.24	78.66
$t_{50\%}$	2.14	1.98	2.02	1.89	2.01	2.14	1.80	1.99	1.96	1.78
$t_{80\%}$	6.30	6.14	6.28	6.02	6.24	6.34	5.98	6.27	6.24	5.90
r^2	0.995	0.990	0.997	0.989	0.991	0.994	0.994	0.984	0.986	0.994
k	2.362	2.512	2.378	2.156	2.318	2.305	2.224	1.214	1.105	1.064
n	0.656	0.641	0.652	0.671	0.661	0.663	0.658	0.726	0.741	0.735

**Q_8 indicates percentage of oxycodone drug release at 8 h; $t_{50\%}$, time required for 50% drug release; $t_{80\%}$, time required for 80% drug release; r^2, correlation coefficient; k, release rate constant; n, diffusion exponent; M, month.*

MUPS tablets of the formulation F4 (18% EC, 30% oxycodone pellets content) compressed at 6 kN were set for the stability for 3 months in three different stability chambers. The appearance of MUPS tablets were found to be unchanged even at the end of 3 months in all stability conditions except 40°C/75%RH, where the color of tablets becomes slightly yellowish, which is negligible. The color change might be related to the excipients, as after 3 months at 40°C/75%RH, the assay of oxycodone was found 97.2%, which is close to the initial value (Table 4). The LOD value was increased slightly from its initial value in all stability conditions (Table 4). No significant change in the assay of oxycodone was observed from the storage conditions (Table 4), which reflects that the formulated MUPS tablets are stable. In each month, the dissolution of oxycodone MUPS tablets was performed for the samples stored in three different conditions. The $t_{50\%}$, $t_{80\%}$, Q_8, release rate constant (*k*), and diffusion exponent (*n*) at different time intervals showed no major difference over the stability period (Table 4). The calculation was performed based on the following equations:

$$t_{50\%} = (0.5/k)^{1/n}$$
$$t_{80\%} = (0.8/k)^{1/n}$$

where *k* is the release rate constant and *n* is the diffusion exponent. The values of *k* and *n* were determined graphically from the following equation (Siepmann & Peppas, 2001):

$$Qt/Q_\infty = k.tn$$

where Qt/Q_∞ is the fraction of drug released at time *t*,

$$\log (Qt/Q\infty) = \log k + n.\log t.$$

To study release kinetics, a graph is plotted between log cummulative percentage of drug release (log ($Qt/Q\infty$)) versus log time (log *t*).

CONCLUSION

Oxycodone pellets coated with aqueous EC dispersion (Surelease E-7-19050) were incorporated into a multiple-unit pellet system providing consistent drug release profiles. Inclusion of 70% cushioning plastically deforming excipient microcrystalline cellulose (Comprecel M102) into the MUPS tablets and application of compression force between 3 and 6 kN resulted in similar dissolution of active substance in comparison with reference matrix tablets. The physical and chemical parameters of the oxycodone MUPS tablets were found consistent over the stability period. The results generated in this study showed that the selected excipients and manufacturing process is suitable to design a new, stable, oxycodone, MUPS, extended-release formulation.

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