

Hot stage extrusion as manufacturing tool for controlled release formulations

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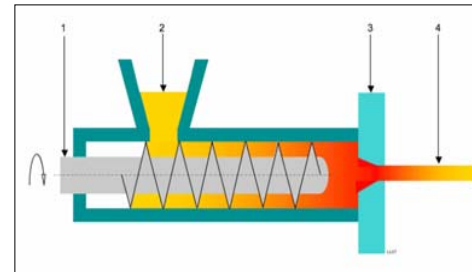
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- Aim of hot-melt extrusion:

embedding of drug in a carrier formulation consisting of one or more meltable substances (and optionally other functional excipients)

- HME process:



1. Screw
2. Hopper
3. Die
4. Extruded material

- Advantages of HME

- anhydrous process, no solvents
- simple process (limited number of process steps, single step?)
- short residence time
- different applications: sustained release, solubility enhancement, taste masking
- different dosage forms (depending on shape of the die and downstream processing equipment): tablets, granules, pellets, films, ...
- continuous process (high throughput)
- on-line monitoring possible
- co-extrusion (e.g. manufacturing of high-precision medical devices)



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- HME formulation

- a. Polymers (thermal binders)

- e.g. methacrylate polymers, cellulose derivatives, PEO, PEG, PVA, waxes, lipids, PVP, copovidone, PEG/PVA graft polymers, poloxamer, PVAc, EVA, silicone, PVP/VA
- requirements:
 - thermoplastic behaviour
 - suitable T_g
 - high degradation temperature
 - low toxicity
 - batch-to-batch consistency

- b. API

- powder properties can affect extrudability
 - thermal stability
 - miscibility/compatibility with polymers
 - particle shape and size
 - flow properties
 - moisture content
 - bulk density

- c. Plasticizers

- e.g. triethyl citrate, PEG, dibutyl sebacate, propyleneglycol, diethyl phtalate, dibutyl phtalate, glycerol monostearate, ...
- reduce T_g and melt viscosity to improve workability and flexibility of polymer
- smooth surface of extrudate (no sharkskin, stick/slip effect)

- Application of HME

- a. Enhancement of solubility and dissolution rate

- formation of solid solution or solid dispersion
 - drugs: itraconazol, antivirals, indomethacin, ...
 - polymers: PVP, PVP/VA, PVP/PEG, poloxamer, ...
 - e.g. Kaletra: lopinavir/ritonavir in HME tablet
 - PVP + itraconazole (solid solution)
 - PVP/VA + nifedipine
 - PVP/PEG + itraconazole (stable amorphous system)
 - miscibility/compatibility between API and polymer

- b. Sustained drug release

- release-controlling polymer (thermoplastic, binder) + API (+ functional excipients)

- case studies:

1. ethylcellulose / xanthan gum / ibuprofen mix via HME
2. ethylcellulose / xanthan gum / metoprolol tartrate mix via HME
3. ethylcellulose / HPMC / metoprolol tartrate mix via HME and injection moulding

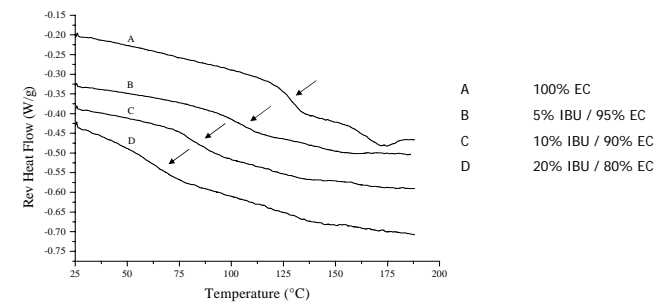
CASE STUDY 1

(Verhoeven et al., EJPB, 2006, 63, 320-330)

- matrix former: ethylcellulose (Ethocel St 10 FP)
- API: ibuprofen (60%, w/w) (mp 76°C)
- functional polymer: xanthan gum
- plasticizer:
- extruder: intermeshing, co-rotating twin-screw extruder
APV Baker MP19 TC-21 L/D-ratio: 25/1
- extrusion settings: powder feed rate 6g/min – screw speed 30 rpm
- extrusion temp: 50°C
- end product: cylindrical mini-tablets (diameter: 3mm / height: 2mm)

- Plasticizing effect

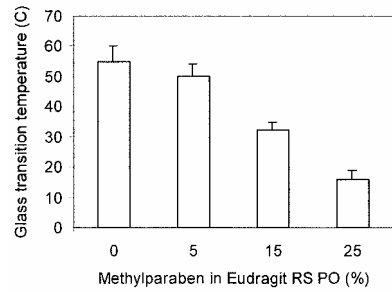
Tg EC: 130°C vs. extrusion temperature: 50°C



⇒ ibuprofen identified as non-conventional plasticizer (De Bradander et al., J. Pharm. Sci, 9, 2002, 1678-1685)

other non-conventional plasticizers:

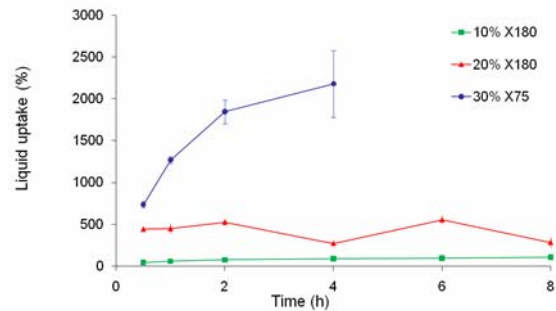
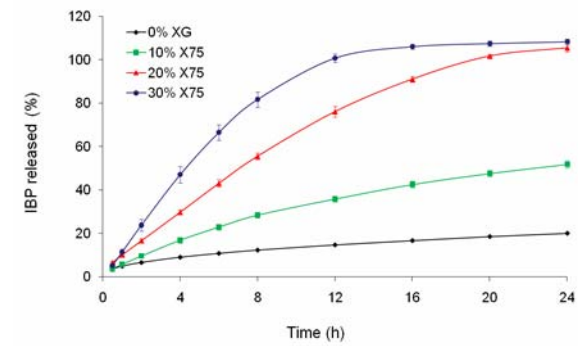
e.g. lidocaine / Eudragit E methylparaben / Eudragit RS
 indomethacin / Eudragit RS ketoprofen / PEO
 guaifenesin / PEO



Wu & McGinity, *EIPB*, 56 (2003) 95-100. Reprinted with permission.

• Concentration of functional excipient

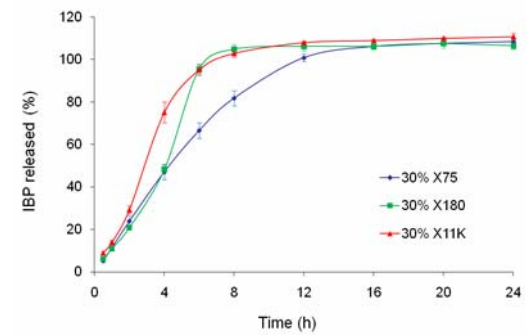
Formulation
 Ibuprofen 60%
 XG 75µm 0-30%
 EC 10-40%

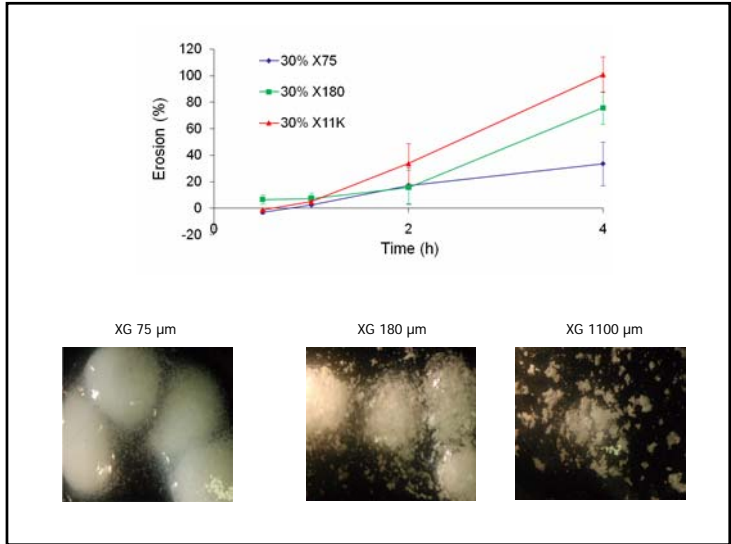


⇒ diffusion-controlled release, but at higher XG content erosion also important

• Particle size of functional excipient

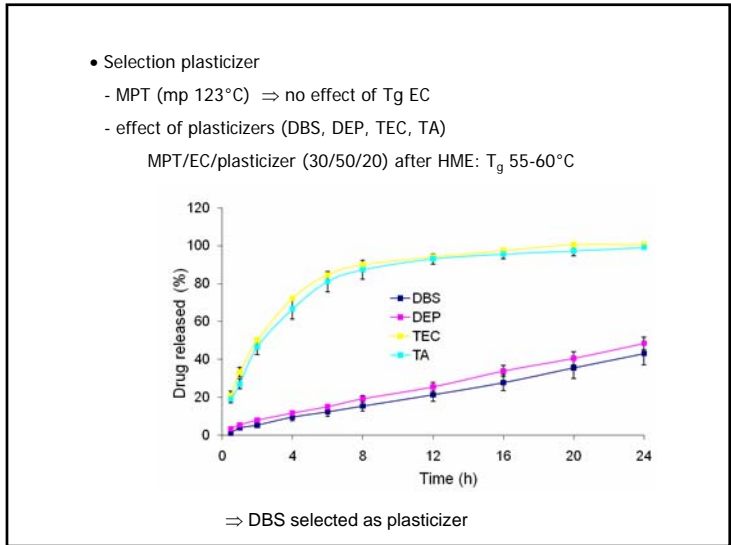
Formulation
 Ibuprofen 60%
 XG 30%
 EC 10%





CASE STUDY 2 (Verhoeven et al., EJPB, 2008, 69, 312-319)

- matrix former: ethylcellulose (Ethocel St 10 FP)
- API: metoprolol tartrate (30%, w/w) (mp: 123°C)
- functional polymer: xanthan gum
- plasticizer: dibutyl sebacate
- extruder: intermeshing, co-rotating twin-screw extruder
APV Baker MP19 TC-21 L/D-ratio: 25/1
- extrusion settings: powder feed rate 6g/min – screw speed 30 rpm
- extrusion temp: 65°C
- end product: cylindrical mini-tablets (diameter: 3mm / height: 2mm)



EC/DBS ratio	Processing temp. (°C)	Torque (%)	Extrudate	Mini-matrices
5/1	80	8	sticky	-
	70	12	smooth	cracks
	60	93	shark skinning	-
3/1	80	16	sticky	-
	70	20	smooth	cracks
	60	31	smooth	cracks
2/1	50	43	shark skinning	-
	80	18	sticky	-
	70	26	smooth	smooth
1.4/1	60	35	smooth	smooth
	50	45	rough	-
	40	78	shark skinning	-
5/1	80	19	sticky	-
	70	22	smooth	smooth
	60	29	smooth	smooth
5/1	50	38	smooth	smooth
	40	59	rough	-

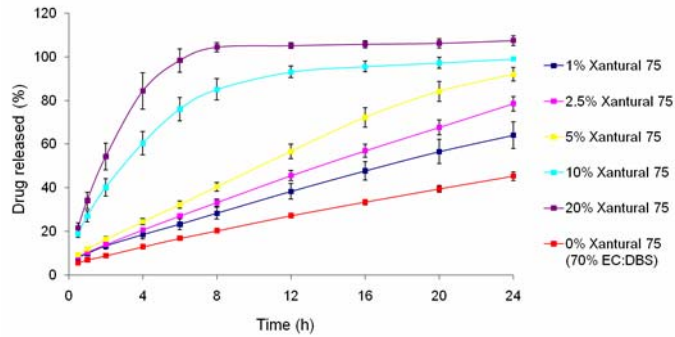
MPT/XG/EC/DBS

ratio: 30/10/50/10 at 70°C

ratio: 30/10/40/20 at 60°C

• Concentration functional excipient

<i>Formulation</i>	
MPT	30%
XG 75 μm	0-20%
EC/DBS (2/1)	50-70%



• Robustness

<i>Formulation</i>	
MPT	30%
XG 75 μm	5%
EC/DBS (2/1)	65%

- effect of shear



⇒ at least one mixing zone required to ensure homogeneity (MPT powder spots at extrudate surface)

⇒ no effect of number of mixing on MPT distribution (using Raman mapping)

- production rate

powder feed rate (25-50 g/min) + screw speed (100-200 rpm)

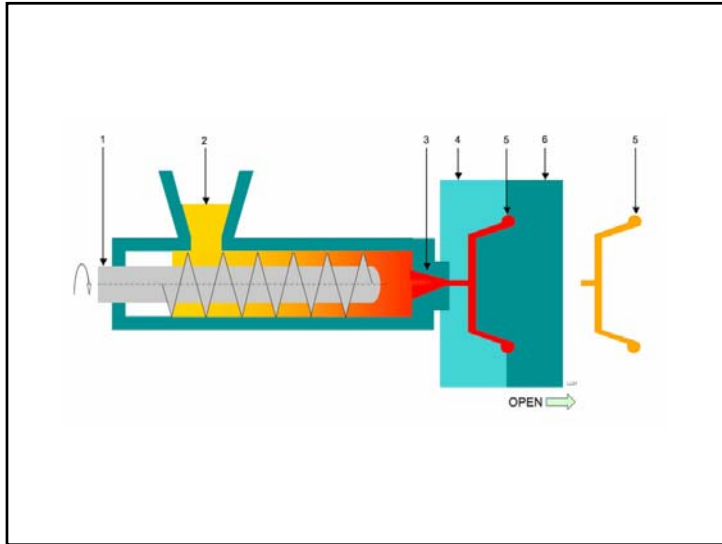
⇒ no effect on extrudate quality

⇒ no effect on drug release profile

CASE STUDY 3

(Quiten et al., EJPB, xxx)

- matrix former: ethylcellulose (Ethocel St 10 FP)
- API: metoprolol tartrate (30%, w/w) (mp: 123°C)
- functional polymer: HPMC
- plasticizer: dibutyl sebacate
- extruder: Haake Minilab II Micro Compounder
- extrusion settings: screw speed 90 rpm
- injection moulder: Haake Minijet System
- injection pressure: 400 bar (10 s) + 200 bar (5 s) as after pressure
- process temp: 110-140°C
- end product: bi-convex tablets (diameter: 10mm / height: 5mm / weight: \pm 375mg)



• Processability

- without plasticizer: only >133°C, but brittle tablets

- + 20% DBS: T_g EC: 53°C

Melt flow index: 110°C → 0.15 g/10min

120°C → 0.73 g/10min

130°C → 4.85 g/10min

140°C → 12.90 g/10min

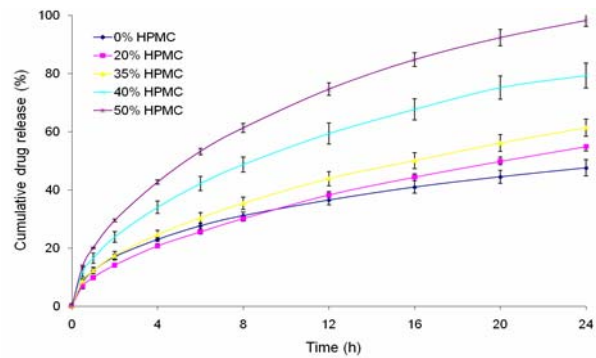
- <110°C: melt viscosity too high ⇒ insufficient flow towards injection mould

- weight uniformity: <1% RSD

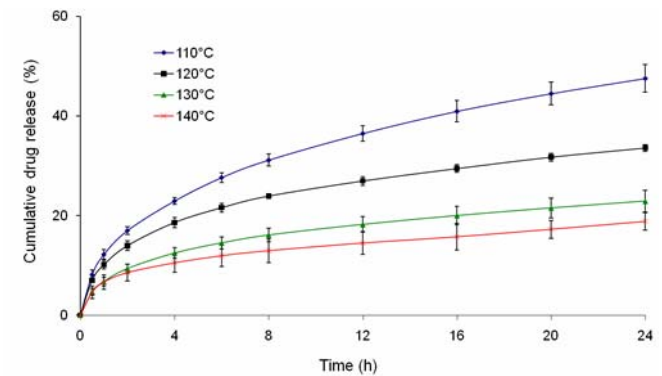
- tensile strength tablets: 1.66 (110°C) – 1.75 (140°C) Mpa

- no degradation of MPT, EC, HPMC and DBS (GPC, TGA, assay)

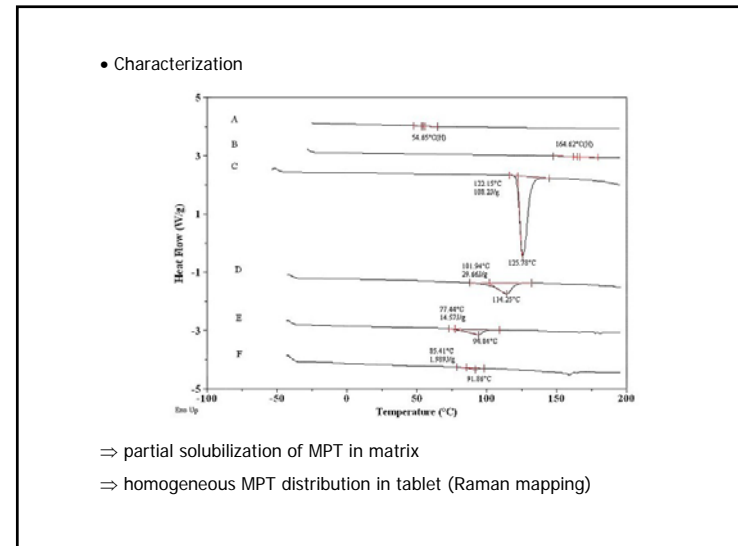
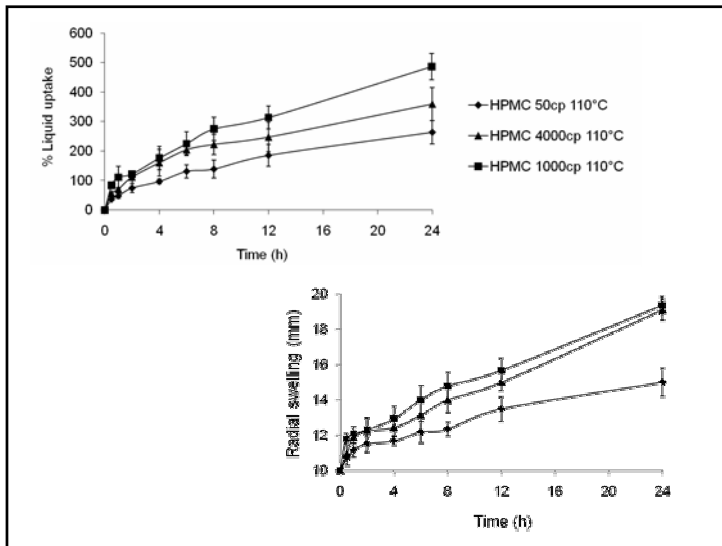
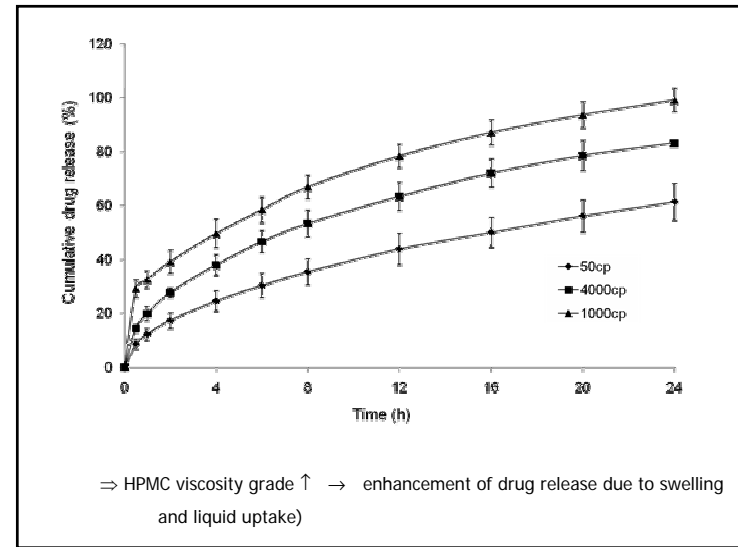
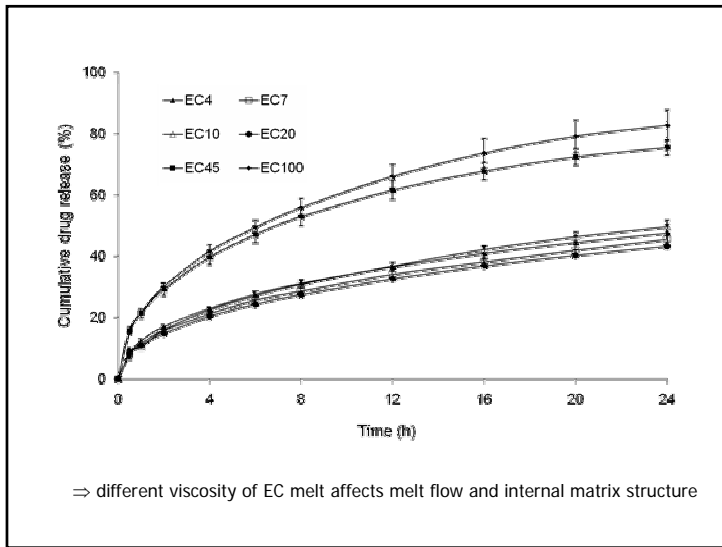
• Drug release



⇒ EC matrix retains integrity but swells due to HPMC



⇒ release via pore diffusion



CONCLUSION

- melt-extrusion (in combination with injection moulding) is a versatile processing technique
- the drug release from sustained release matrices manufactured via HME (+ IM) can be modified depending on formulation (matrix former, drug and functional excipient).
- depending on the formulation and manufacturing technique, different parameters need to be optimized.