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Development of sustained release gastroretentive floating tablets using HME coupled 3D printing: A QbD approach



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PURPOSE

The main objective of this study was to develop sustained release gastroretentive floating tablets using fused filament fabrication (FFF) 3D printing and evaluate the effect of formulation and process variables on in vitro drug release characteristics using Quality by Design (QbD) approach.

METHODS

Hot Melt Extrusion: Hydroxypropyl methylcellulose (HPMC E5), ethyl cellulose (EC-N14), and acetaminophen (APAP) (model drug) were blended using maxblend™ (globepharm, new brunswick, NJ, USA) at 25 rpm for 15 minutes. A 11mm twin screw extruder (thermo fisher scientific, waltham, MA, USA) was used to extrude cylindrical filaments with a 1.75mm diameter to be used as feedstock material for 3D printing.

3D Printing: The tablets were designed as hollow cylindrical objects (d=12.4mm, h=5mm) to decrease density and float in gastric medium, using tinkercad™ free online software (autodesk, CA, USA). Combining both these digital files and previously extruded filaments, the gastroretentive floating tablets were prepared using a FFF based 3D printer (prusa i3 3D desktop printer, prusa research, prague, czech republic). The formulation variables (% drug load, EC concentration) and process variables (shell thickness) were chosen as independent variables and % drug release at 2h, 6h and 10h were chosen as dependent variables (Table 1, 2 & 3.). A response surface method with three-factor, three-level box-behnken design was applied for the optimization of sustained release floating tablets.

Characterization: Thermal stability of polymers in the study was assessed using thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). Mechanical properties of the extruded filaments were determined using a texture analyzer (TA-XT2i analyzer, texture technologies, MA, USA). (Figure 1.). The printed tablets were evaluated for in vitro drug release and floating ability in 0.1N HCl dissolution media. (Figure 2.).

RESULTS

Table 1. DoE independent and dependent variables

Variables	Unit	Lower limit	Upper limit
Drug load	% (w/w)	15	35
Shell thickness	mm	0.8	1.6
EC	% (w/w)	0	40

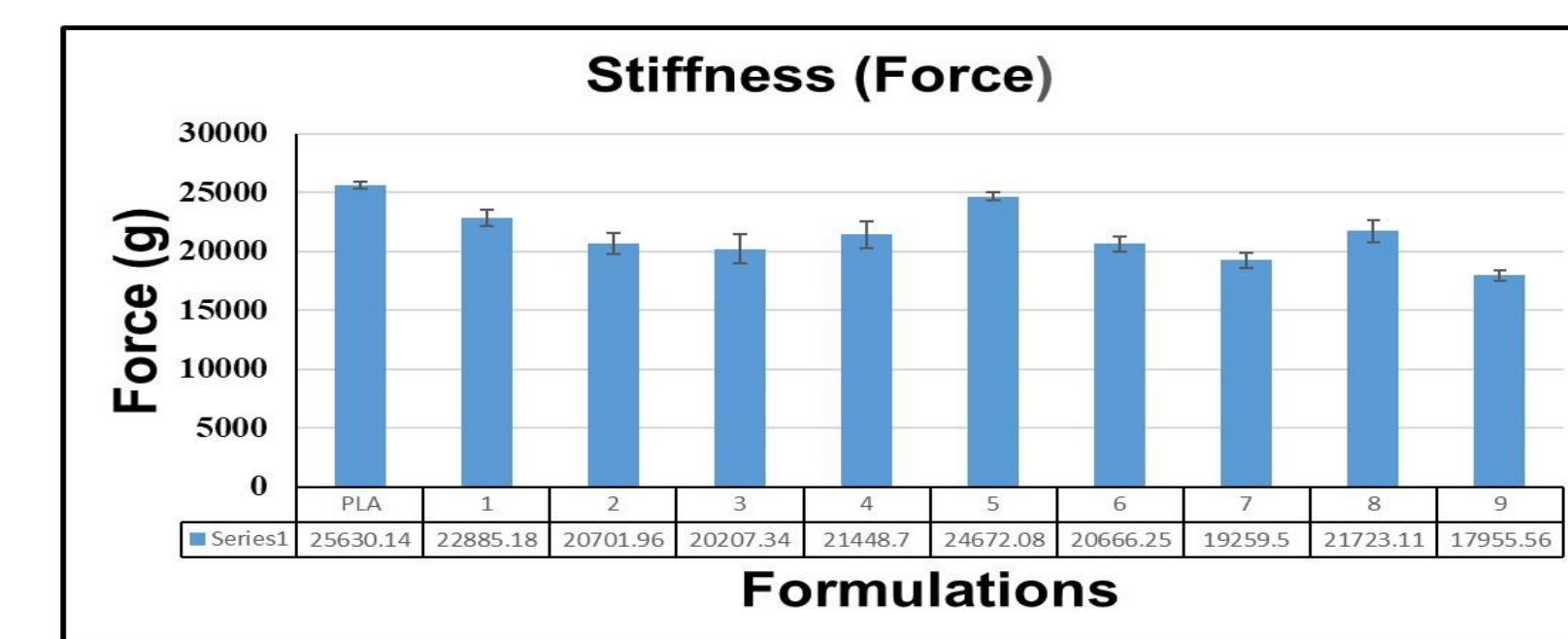


Figure 1. Stiffness values of all the extruded filaments analyzed by Repka-zhang test

Table 3. Cumulative drug release values of all the formulations at 2h, 6h and 10thh

Run. No	Dissolution 2h	Dissolution 6h	Dissolution 10h
1	36.8	66.6	83.7
2	48.2	83.0	98.0
3	46.7	84.8	100.0
4	21.5	40.9	56.8
5	34.2	65.0	88.6
6	41.6	71.7	93.0
7	43.2	89.4	100.3
9	57.5	96.0	100.0
10	39.1	70.2	92.6
11	33.3	62.8	78.7
12	31.1	59.7	78.8
14	26.4	47.6	65.8
15	43.8	70.7	84.5
16	38.0	65.3	84.1
17	38.9	68.9	92.9

Table 2. Runs suggested by the DoE software

Run. No	APAP (%)	Shell thickness (mm)	EC(%)
1	25	1.2	20
2	25	1.2	0
3	35	1.6	0
4	15	1.6	40
5	35	1.6	40
6	35	1.2	20
7	15	0.8	0
9	35	0.8	0
10	15	1.6	0
11	25	1.6	20
12	25	1.2	40
14	15	0.8	40
15	35	0.8	40
16	15	1.2	20
17	25	0.8	20

Table 4. Model summaries of the QbD experiments

	Dissolution at 2h		Dissolution at 6h		Dissolution at 10h	
	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value
Intercept	37.45	-	67.03	-	81.92	-
A-API	5.57	0.0002	7.5	0.0002	3.77	0.0009
B-Shell thickness	-3.49	0.0027	-4.9	0.0021	-5.56	0.0636
C-EC	-7.77	< 0.0001	-13.96	< 0.0001	-14.5	< 0.0001
AB	-1.43	0.1418	1.13	0.3591	-0.6238	0.0983
AC	1.02	0.2776	3.26	0.0257	2.21	0.0053
BC	0.0626	0.9442	2.25	0.0923	-2.87	0.8058
A ²	1.89	0.2451	1.14	0.587	-4.36	0.6255
B ²	-1.86	0.2518	-1.47	0.4839	-7.12	0.5272
C ²	1.7	0.2911	3.96	0.0875	-4.54	0.6767
Adj. R ²	0.8991	-	0.8876	-	0.7807	-
Pre. R ²	0.8542	-	0.8152	-	0.6120	-
F-Value	20.28	-	30.76	-	16.25	-
Model p-value	0.0003	-	< 0.0001	-	0.0007	-

- ✓ The coefficients of % APAP are positive implying that drug dissolution increases with increase in API load.
- ✓ Whereas the coefficients of both shell thickness and % EC are negative indicating drug dissolution decreases with increase in shell thickness or % EC.
- ✓ % EC had greatest effect on drug release profiles whereas shell thickness had the least effect.
- ✓ Both % APAP and % EC significantly influenced the drug release at 2h, 6h and 10h (p<0.05), where as shell thickness had significant effect at only at 2h and 6h and lost effect at 10 h (p=0.0636).(Table 4.)
- ✓ No interaction is seen between all three factors (p>0.05), but at 10th h, when shell thickness lost effect, there is an interaction between drug load and % EC (p=0.0053). (Table 4.).
- ✓ APAP, is freely water-soluble drug, so as the % APAP increased in formulation, the drug release increased.
- ✓ EC is a hydrophobic and water insoluble polymer, so as % EC is increased, drug release decreased
- ✓ Shell has separate fill pattern and denser structure compared to core of tablet. So higher shell thickness successfully prevented the entry of dissolution media for longer time and resulted in reduced drug release.

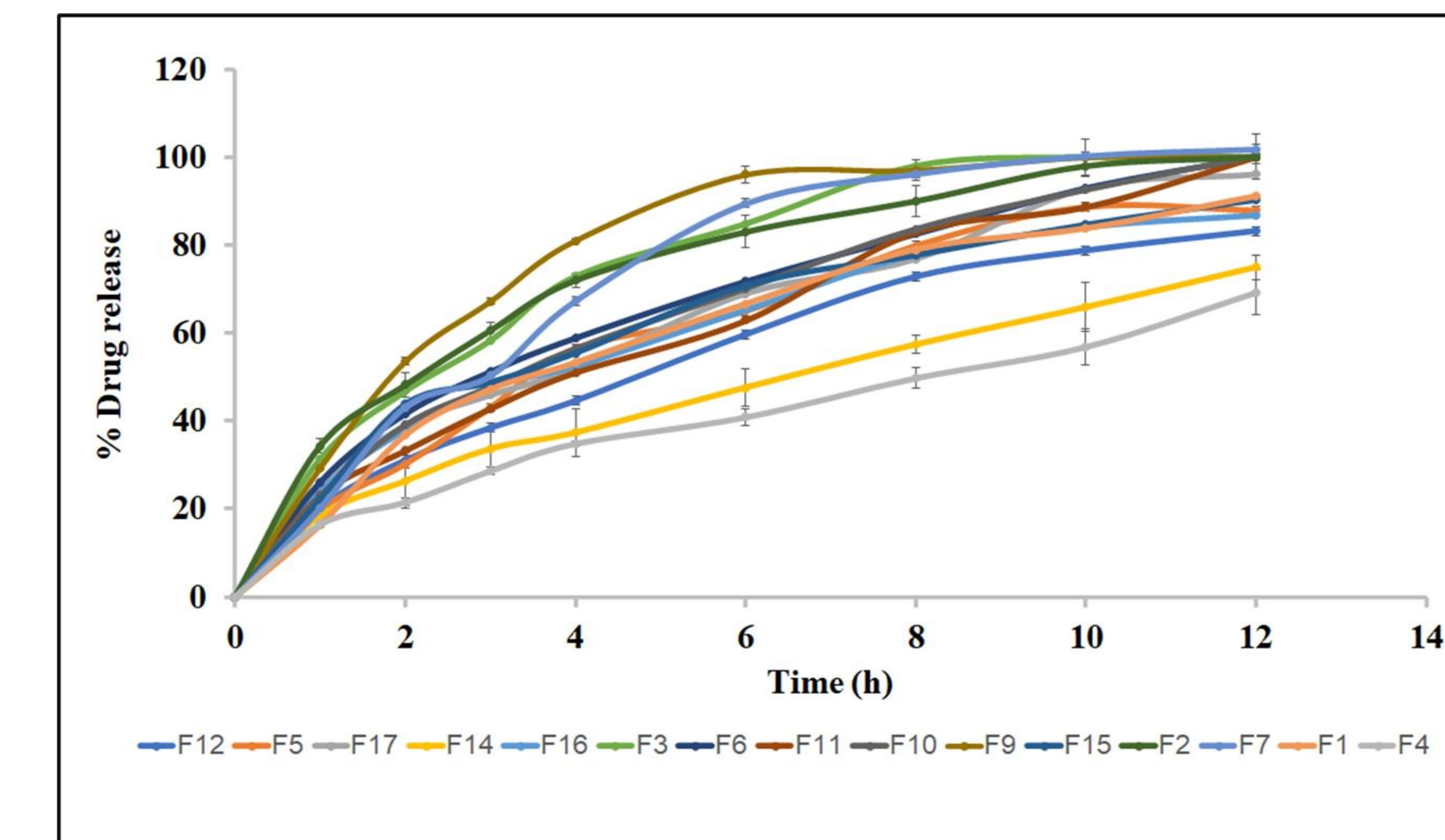


Figure 2. In vitro drug release profile of sustained release floating tablets in 0.1N HCl

CONCLUSIONS

- ✓ Filaments suitable for FFF 3D printing were successfully fabricated using different ratios HPMC, EC and APAP.
- ✓ All the three independent factors studied had significant effect on drug release profiles.
- ✓ QbD was applied to assess the effect of formulation and process parameters on in vitro drug release characteristics.
- ✓ Sustained release gastroretentive floating tablets were prepared with HME coupled 3D printing.
- ✓ All the printed tablets exhibited good floating behavior throughout the dissolution studies.
- ✓ FFF 3D printing combined with QbD is a novel viable tool for fabricating customized dosage forms for personalized pharmacotherapy.

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