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Formulation development of loratadine immediate-release tablets using hot-melt extrusion coupled with 3D printing technology

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PURPOSE

The main goal for this study is to develop immediate release Fused Deposition Modeling (FDM) 3D printed loratadine tablets using hot-melt extruded filaments..

OBJECTIVE(S)

- Optimize the formulation composition and HME processing parameter to extrude filaments that can be fed into an FDM-3D printer and perform as an immediate release.
- Designing the 3D printed tablet and optimize the 3D printing sittings.
- Evaluate the 3D printed tablets.

METHOD(S)

Formulation optimization and HME: Loratadine was used as a model drug with 10% (w/w) drug loading. Crospovidone (Polyplasdone XL) and croscarmellose sodium were used as super-disintegrants, to facilitate tablets` disintegration, dissolution, and the release of loratadine from the formulations. Mannitol was used as a pore-forming agent to enhance the dissolution. Polyethylene Glycol 1500 (PEG-1500) was used as a plasticizer. Polyethylene oxide N80 (PEO N80) and hydroxypropyl cellulose EF (HPC-EF) were used as polymeric carriers. The physical mixtures of the selected formulations **(Table1)** were then extruded using an 11 mm twin-screw co-rotating extruder (Process 11 twin-screw extruder Thermo Fisher Scientific, Waltham, MA, USA).

Three-point bend test: Performed using a texture analyzer (TA-XT2i Texture Analyzer by Stable Micro Systems, UK), to evaluate the printability of the extruded filaments. The filament placed on a sample holder with a 25 mm gap, the blade speed was set at 10 mm/s for pre-test speed, test speed, and post-test speed, the distance at 10 mm, and the trigger force at 5 g.

FDM-3D printing: The printable filaments were printed using an FDM-3D printer (Prusa i3 3D desktop printer, Prusa Research, Prague, Czech Republic) with 40% to 60% infill, and Grid pattern

Weight variation: Ten tablets of each formulation were weighed using an analytical balance.

Drug assay: To evaluate drug content and uniformity of physical mixtures, filaments, and tablets.

Disintegration test: The disintegration time was evaluated using a disintegration apparatus (Dr.Schleuniger® Pharmatron DT2-IS Disintegration Tester, Uttigenstrasse 28, 3600 Thun, Switzerland). 1 L of 0.1 N HCl (pH 1.2) medium was used and maintained at 37 °C for 15 minutes.

***In-vitro* drug release study:** The release profile of printed tablets was evaluated using a United States Pharmacopeia (USP) dissolution apparatus II (Hanson Research Virtual Instruments SR8 Plus, Los Angeles, CA). The dissolution medium was 900 mL 0.1 N HCl (pH 1.2), maintained at 37°C and 50 rpm. A sample of 2 mL was withdrawn at time points 3, 6, 10, 15, 11, 30, 45, and 60 minutes, centrifuged for 10 minutes at 25°C at 13,000 rpm, and then analyzed using HPLC.

HPLC analysis: Performed to evaluate drug assay and *In-vitro* drug release, using Waters HPLC-UV system (Waters Corporation, Milford, MA, USA). Phenomenex C8 column (5 microns, 150 * 4.6 mm) was used and the test conditions were set up as follows: column temperature 30°C, flow rate 1mL/minute, injection volume 10µL, loratadine detection wavelength at 247 nm. The mobile phase consisted of phosphate buffer pH 6 methanol (20:80).

Differential scanning calorimetry (DSC): The physical mixtures, filaments, and 3D-printed tablets were analyzed using a (TA DSC 25) with a heating rate of 10 °C/min from 25 to 250 °C, to determine the physical state of loratadine.

Fourier transform infrared spectroscopy (FTIR): Performed to investigate the interactions between loratadine and the polymeric carriers using an Agilent Cary 660 (Agilent Technologies, Santa Clara,CA, USA).

RESULT(S)

All formulations were successfully extruded in a four conveying zones and three mixing zones. The filaments were white to off-white in color. The torque and die pressure were within an acceptance range with 50 rpm screw speed**.** Based on the filament's mechanical properties, six filaments (F3, F5, F6, F7, F9, F10) out of ten were printable **(Table 2).** Greater breaking stress is a sign of harder filament texture. While a longer breaking distance implies a softer filament. Higher breaking stresses or breaking distances indicate increased brittleness. When the filament has a higher stiffness value (*k*), printability will be improved, as the resistance of filament to deformation increases. The loratadine DSC thermograms showed an endothermic melting peak at 134.5 °C. On the other hand, this endothermic peak disappeared in the extruded filament as well as the 3D-printed tablets indicating complete solubilization of loratadine in the polymeric carrier for all 6 formulations **(Figure 1).** Loratadine has characteristic absorption bands at 1699 cm−1 (C=O stretching), 1433 cm−1 (-C-O stretching), 1219 cm−1 (Aryl -C-N stretching), and 996 cm−1 (Aryl C-Cl stretching). In **Figure 2** when comparing pure loratadine with the extrudate, (C=O) peak shifted to a higher wavelength, (-C-O) band broadened and shifted to a higher wavelength indicating that loratadine interacted and solubilized within the polymer. The tablets were printed in a grid pattern and with 40% to 60% infill to accelerate the drug release **(Figure 3).** The target weight was 100 mg and most of the tablets had a weight between 95 and110 mg. Loratadine content of 3D printed tablets were 87.24%-113.90%. All 3D printed tablets disintegrated within 15 minutes. The drug release from the printed tablets "F3(40%infill), F5(40%infill), F9(40%infill), F10(40%infill)" showed 89.2%, 86.1%, 85.8%, and 96.8% respectively in 30 minutes **(Figure 4).** .

Table 1. Loratadine formulations` compositions.

	Loratadine (w/w %)	PEO N80 (w/w %)	HPC-EF (w/w %)	Mannitol (w/w %)	PEG1500 (w/w %)	Croscarmellose Sodium (w/w %)	Polyplasidone XL (w/w %)
F1	10	35	35	0	10	0	10
F2	10	0	70	0	10	0	10
F3	10	70	0	0	10	0	10
F4	10	27.5	27.5	15	10	0	10
F5	10	0	55	15	10	0	10
F6	10	55	0	15	10	0	10
F7	10	0	65	15	10	0	0
F8	10	65	0	15	10	0	0
F9	10	0	55	15	10	5	5
F10	10	55	0	15	10	5	5

Figure 1. DSC thermogram of F3

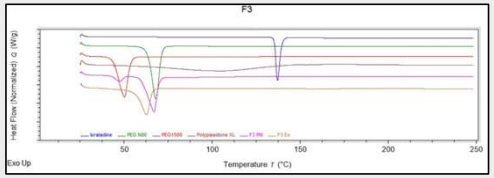


Figure2. FTIR spectra for F3, over a 600–4000 cm−**1** range

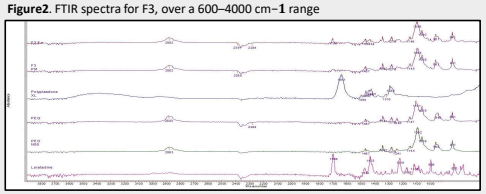


Table 2. 3-point bend test.

Filament code	Time (sec.)	Breaking Force (g)	Breaking Distance (mm)	Breaking Stress (g/mm²)	K (g/mm³)	Printability
F1	1.14±0.07	210.35±10.66	6.15±0.14	87.46±5.00	85.78	Failed
F2	1.07±0.07	282.2±25.32	6.21±0.57	111.57±15.80	410.79	Failed
F3	1.90±0.08	155.77±25.45	2.10±0.69	77.24±10.58	190.61	Printable
F4	1.03±0.01	164.24±8.56	7.00±0.19	63.80±9.21	201.27	Failed
F5	1.04±0.09	301.43±8.9	6.74±0.21	125.34±4.14	396.48	Printable
F6	1.67±0.02	197.77±11.37	0.40±0.25	82.23±5.29	87.85	Printable

Figure 3. 3D-printed tablets, grid pattern with different %infill.

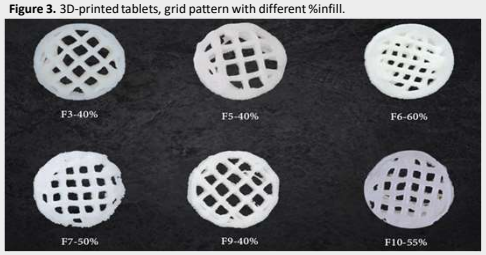
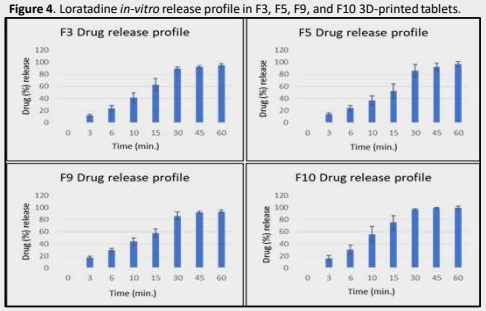


Figure 4. Loratadine *in-vitro* release profile in F3, F5, F9, and F10 3D-printed tablets.



CONCLUSION(S)

Formulation development of loratadine immediate-release tablets using hot-melt extrusion coupled with FDM 3D-printing technology was studied and presented. The HME process was shown to have a great potential to develop filaments which were suitable for FDM-3D printing of immediate release loratadine tablets. The percent infill, printing pattern, and the formulation compositions are critical variables in the development of an immediate-release for loratadine 3D printed tablets. An accurate tablet weight can be achieved using FDM-3D printing technology.

Extruded filaments from formulation numbers F3, F5, F6, F7, F9, and F10 were printable, and the printed tablets except for F7 (no super-disintegrant) met the dissolution criteria of 80% released within 30 minutes. F3 and F10 containing polyplasdone XL alone in F3 and a combination of polyplasdone XL and croscarmellose sodium as a super-disintegrants in F10, and PEO N80 as a polymeric carrier showed the fastest loratadine disintegration and dissolution profile. When comparing all formulations, F10 had faster dissolution profile, in this formulation the super-disintegrant used was a combination of polyplasdone XL (5% w/w) and croscarmellose sodium (5% w/w). The disintegration times for the printed tablets ranged from 8 to 12 minutes for the immediate-release printed tablets. Loratadine content was within the acceptance range in both the extruded filaments and the 3D printed tablets.

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