Exploring Clinical Outcomes of 3D Printed Tablets by Physiologically based Pharmacokinetic Modeling

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Introduction

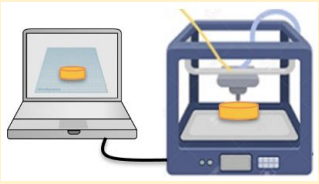
- FDM 3D printing (3DP) is a well-known technique to prepare oral solid dosage forms. However, very little is known about their clinical performance as no clinical studies have been conducted.
- In this study, we attempt to understand the fate of 3DP tablets inside the gastrointestinal tract by physiologically based pharmacokinetic modeling.

Study Objective

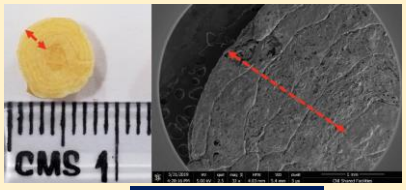
- The aim of the study is to use gastrointestinal simulation technology to investigate and understand the clinical efficacy of FDM 3DP tablet.

Results/Discussion

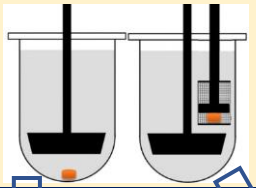
- All 3D printed tablets demonstrated consistent reproducibility with uniform weight and drug content.
- DSC showed minimum crystallinity with a melting endotherm at 195ºC.
- PXRD showed amorphous nature as a result of solid dispersion formation.
- FTIR showed no chemical interactions between drug and excipients.
- Permeability studies through Caco2 cell monolayer showed significant CBZ permeation from all tablets with no hindrance due to tablet components.
- The in-vitro release study completed using the USP-II dissolution apparatus showed slower release as compared to the PD pertaining to the external force produced by the actuator to simulate the peristaltic movement inside the GIT.
- Comparison of the simulation study data from GastroPlus™ software against the clinical pharmacokinetic data for CBZ controlled release tablet showed no appropriate correlation which can be attributed to a distinct release mechanism for 3DP tablets, therefore it cannot be considered for a biowaiver extension.



3D Printer



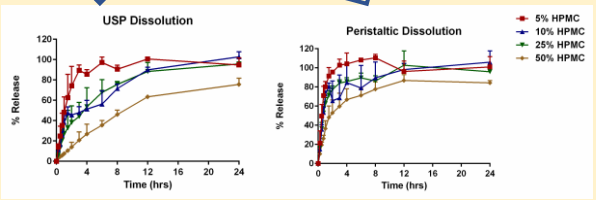
3D Printed Tablet



USP & Peristaltic Dissolution

S. No.	HPMC %	Weight variation (mg)	% Drug Content
1	0	132.6 ± 7.3	96.7 ± 3.5
2	5	147.1 ± 18.7	88.8 ± 1.8
3	10	114.6 ± 20.0	91.5 ± 8.8
4	25	135.7 ± 8.1	99.9 ± 7.6
5	50	144.0 ± 10.7	97.6 ± 1.6

Formulation table with % HPMC (w/w), Weight variation and % Drug content



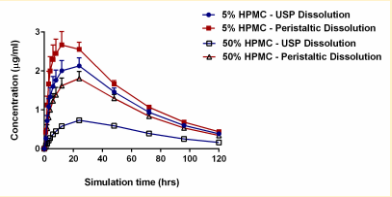
In-vitro Release Data

Gastroplus Simulation Study

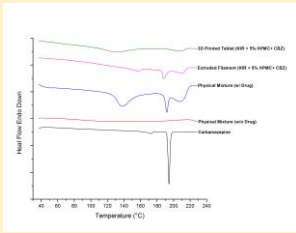
3DP Tablet	C_{max} (ug/ml)	t_{max} (hours)	$AUC_{0-\infty}$ (µg h/ml)
0% HPMC - USP Dissolution	2.17 ± 0.23	19.66 ± 1.20	164.70 ± 14.30
10% HPMC - USP Dissolution	1.79 ± 0.09	21.56 ± 0.41	140.48 ± 6.13
25% HPMC - USP Dissolution	1.46 ± 0.36	23.00 ± 1.50	116.90 ± 26.57
50% HPMC - USP Dissolution	0.73 ± 0.04	25.70 ± 0.10	61.78 ± 3.72

	C_{max} (mg/L)	t_{max} (h)	$AUC_{0-\infty}$ (µg h/mL)
CBZ IR product (test)	4.74 ± 1.27	8.6 ± 2.8	259.03 ± 69.02
CBZ IR product (reference)	4.34 ± 1.24	9.7 ± 4.5	259.15 ± 63.97
CBZ CR product (test)	3.88 ± 0.90	14.7 ± 7.2	241.94 ± 58.31
CBZ CR product (reference)	3.65 ± 1.42	14.3 ± 9.3	236.80 ± 87.23

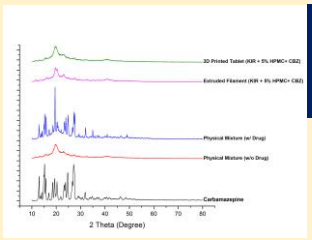
Simulated Clinical Pharmacokinetic Parameters



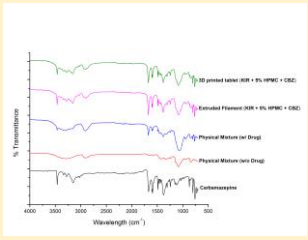
Concentration – Time curve



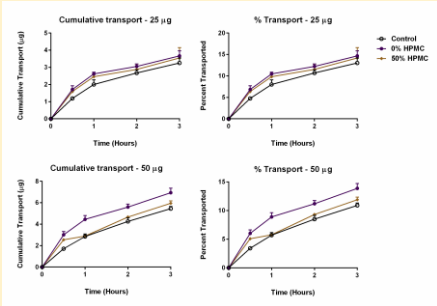
Differential scanning calorimetry (DSC)



Powder X-ray diffraction (PXRD)



Fourier-transform infrared spectroscopy (FTIR)



Permeability Studies