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Formulation Design and Evaluation of 3D Printed Tablet of Cinnarizine by Fused Deposition Modeling Technique

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Abstract

This study aimed to explore the feasibility of fused deposition modeling (FDM) 3D printing to prepare tablets of cinnarizine. Cinnarizine is an antihistamine drug, was chosen as a model drug to investigate, and was successfully loaded into commercial polyvinyl alcohol (PVA). The tablet was designed by AutoCAD then designed tablet was sliced by the Cura Ultimaker 4.4 software. The filaments were then printed into hollow structured tablets with 0% infill than Cinnarizine drug was added on the hollow tablet and closed the upper surface with help of a 3D printer. The drug-loaded 3D printed tablet was evaluated for drug release under in-vitro dissolution conditions, and we found the release profile fit Korsmeyer–Peppas release kinetics.

Keyword: 3D Printer, Fused dipostion modeling, 3D Printed Tablet.

Introduction

Three-dimensional (3D) printing is a process of creating 3D objects, where materials are deposited layer over layer using a computer-driven process based on a digital model. In the pharmaceutical field, it has the potential to arriving individualized and on-demand medications to avoid variable effects and adverse reactions during drug therapy. It also provides hopes for formulating patient-centric fixed-dose combinations to reduce multiple daily dosing and thus improve patient compliance. Various techniques for 3D printing, such as fused deposition modeling (FDM), binder deposition, inkjet printing, material jetting, powder bed fusion, photopolymerization, pen-based 3D printing and molding, have been reported in the literature [1,2,3].

First orally disintegrating 3D printed tablet, Spritam® (levetiracetam), by U.S. Food and Drug Administration in 2015, the interest in the pharmaceutical sector for 3D printing has been growing very rapidly. However, Spritam® was prepared by spraying the binder solution on successive layers of powder (powder beds) to prepare a loose compact, and, as indicated by Sadia *et.al.* [1,4,5,6].

Three dimensional printing technology is a novel rapid prototyping technique in which solid objects are constructed by depositing several layers in sequence. Rapid prototyping involves the construction of physical models using computer-aided design in three dimensions. It is also known as additive manufacturing and solid freeform fabrication. 3D printing technology has enabled unprecedented flexibility in the design and manufacturing of complex objects, which can be utilized in personalized and programmable medicine. It is a nominal strategy to overcome some challenges of conventional pharmaceutical unit operations [3,10].

3D printing technology offers unique benefits to drug products manufacturing, when compared to traditional methods notably, the capacity of designing personalized pharmaceutical forms with flexible dosage, different shapes, multiple active pharmaceutical ingredients (even incompatible ones), and modulated release kinetics.

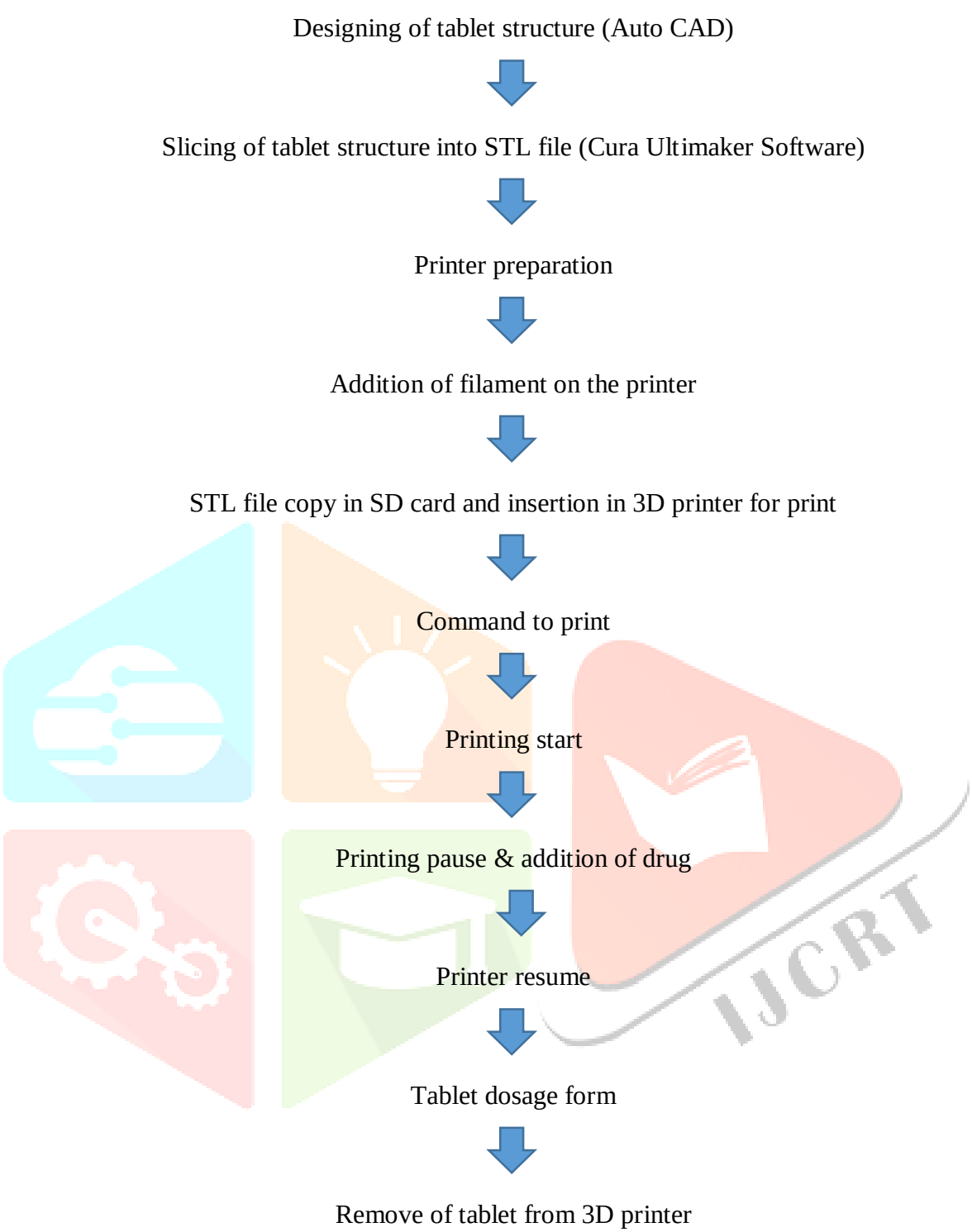
Moreover, the most diversified and sophisticated drug delivery devices for oral, dermal, and implantable administration can be produced with high accuracy using 3D printers [1,3].

MATERIAL AND METHOD

Material

Cinnarizine drug was gifted by Geno pharmaceutical pvt. Ltd., Goa and PVA filament was purchased from WOL 3D, Mumbai.

Designing and Printing of 3D Printed Tablet



3D printing process

3D printing of tablet was prepared by the following step. In figure 1 3D cad file/ STL format was designed by the CAD software for slicing. In figure 8.5 Slicing / G-Code file Format was sliced by slicing software. It was helping to maintain the size of the structure for printing. In figure 2 3D Printing of structure of sliced file format firstly print hollow tablet than drug was added and cover the tablet with help of a 3D printer.

Figure 1. 3D CAD file / STL file format

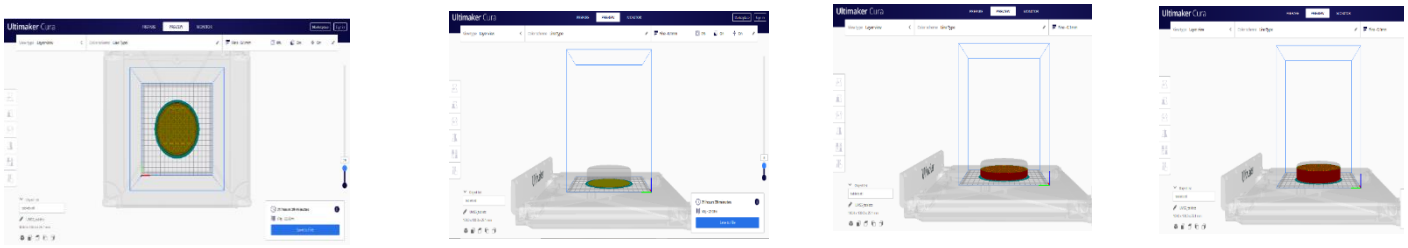


Figure 2. Slicing / G-COAD file format

Printing of hollow tablet **Addition of drug** **Final tablet**

Figure 3. 3D printing

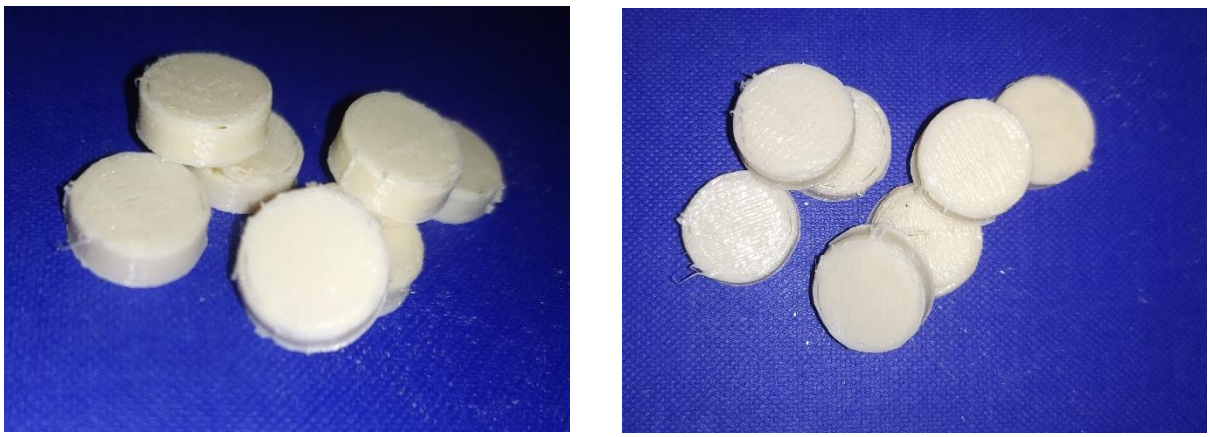


Figure 4. 3D Printed Tablets

Formula for 3D Printed Tablet

Table 1. Formula for 3D printed Tablet

S. No.	Name of Ingredient	Quantity taken	Uses
1	Cinnarizine	50 mg	API
2	Polyvinyl alcohol	470 mg	Polymer

Melting Point

A small amount of powder and Poly-vinyl alcohol (PVA) was located in a fusion tube. That the tube was located in the melting point apparatus containing castor oil. The temperature of the castor oil was gradually increased automatically and the temperature was recorded when all the powder gets melted[32].

Loss on Drying

Loss on drying measured by IR moisture balance. Firstly calibrated the instrument by knob then taken 5.000 gm cinnarizine (powder) and set the temperature at 100ºC to 105ºC for 5 min. and constant reading set the knob and check % moisture[32].

% Loss of Drying = Mass of water in sample / Total mass of wet sample X 100

Thermal Analysis

Thermograms were recorded using a differential scanning calorimeter. Cinnarizine (5-10 mg) were weighed and hermetically sealed in flat bottomed aluminium pans. These samples were heated over a temperature range of 0-300ºC in an atmosphere of nitrogen (200 ml/min) at a constant rate of 10^0C per minute, with alumina being the reference standard[33].

Fourier-Transform Infrared Spectroscopy (FTIR)

Fourier-transform infrared spectroscopy (FTIR) is a technique used to obtain an infrared spectrum of absorption or emission of a solid, liquid, or gas. An FTIR spectrometer simultaneously collects high-resolution spectral data over a wide spectral range. This confers a significant advantage over a dispersive spectrometer, which measures intensity over a narrow range of wavelengths at a time. The area from 0.8µ to 2.5µ is called near Infra-red and that from 15µ to 200µ is called far infra-red region.

Identification cinnarizine was done by FTIR Spectrometer with respect to a marker compound. Cinnarizine was obtained as a white or almost white crystalline powder. It was identified from the result of the IR spectrum as per specification[34].

CHARACTERISATION OF THE 3D PRINTED TABLETS PROPERTIES

Weight Variation

Twenty tablets were selected randomly from formulation and the average weight was determined. The tablets were weighed individually and compared with the average weight. IP/BP & USP limits for tablet weight variation is given below[35].

Average weight of tablet = Total weight of 20 tablets / 20

Weight variation = (weight of each tablet - average weight of tablet) X 100 /average weighy

Friability

Weight accurately 10 tablets and placed all tablets in friabilator for 100 rotations or 4 min at 25 rpm. After that removed all tablet and polished with a brush and weighted. Then calculated the % friability. Rotation: - 25 rpm or 100 rotations[35].

Friability (%) $= W_I - W_f / W_I$ **X** 100

Where,

W_I = Weight of Tablets (Initial / Before Tumbling)

W_f = Weight of Tablets (After Tumbling or friability)

Hardness

The hardness of the three tablets was determined using the Monsanto hardness tester and Pfizer hardness tester[35]. Results were expressed in Kg/cm^2

Drug Content

Weigh out 100 mg of cinnarizine was dissolved in 25 ml of 0.1N HCl. Make sure to dissolve it completely. Take 1 ml solution from upstairs preparation and diluted it up to 10 ml of 0.1N HCl. Set up the apparatus to wavelength 28 nm and established to auto zero. Took sample into cuvette and started analysis[36].

Drug Content (mg) = Drug Concentration X Dilution Factor

% Drug Content = (Drug Content / Label Claim) X 100

In-Vitro Drug Release

Dissolution apparatus- Type II apparatus (Basket Type)

Dissolution medium- 0.1N HCl

Rotating speed-100 rpm.

Volume- 900 ml

Temperature - 37±.0.5ºC

Height of dissolution jar- 168+8mm[37].

Drug Release Kinetic

The formulation of the 3D printed tablet was subjected to *in-vitro* release studies, using dissolution apparatus, 0.1 N HCl. The results obtained for *in-vitro* release studies were fitted in different models of the data treatment as follows;

- Cumulative percent drug released vs. time (zero-order rate kinetics)
- Log cumulative percent drug retained vs. time (First order rate kinetics)
- Log cumulative percent drug released vs. square root of time (Higuchi's classical diffusion equation)
- Log of cumulative % release vs. log time (Korsmeyer and peppas exponential equation) [38].

RESULT

Melting Point of Cinnarizine

Melting point determines by digital melting point apparatus at 119-122ºC of cinnarizine. In Indian Pharmacopoeia the reported melting point of cinnarizine was 117-121ºC. We observed cinnarizine melting point was 119-122ºC. That was closed to the reported cinnarizine drug that means it was possible to it was cinnarizine.

Melting Point of PVA

The melting point was determined by digital melting point apparatus at 196-200ºC for PVA Filament. According to the handbook of pharmaceutical excipient PVA, the melting point was 190-200ºC but our PVA filament melting point was found to be 196-200ºC.

Loss on Drying

The percentage of loss on drying was found to be 0.040±0.115% for Cinnarizine. Cinnarizine was not cross the acceptance limit of percent loss of drying. It means cinnarizine was not contained more moisture. It shows that cinnarizine was avoided dangerous cross-contaminate with excipients and other drugs in the formulation.

Table 2. Melting point and loss on drying

S. No.	Melting Point of Cinnarizine	Melting Point of PVA	Loss on Drying
1	119-122ºC	196-200ºC	0.040±0.115

Determination of λ_{max} of Cinnarizine in 0.1N HCl

The wavelength of maximum absorbance (λ_{max}) of cinnarizine was found to be 248 nm in 0.1N HCl. The calibration curve for cinnarizine in 0.1 N HCl and methanol is shown in the figure. Absorbance and concentration for cinnarizine were found to be linear in the concentration range.

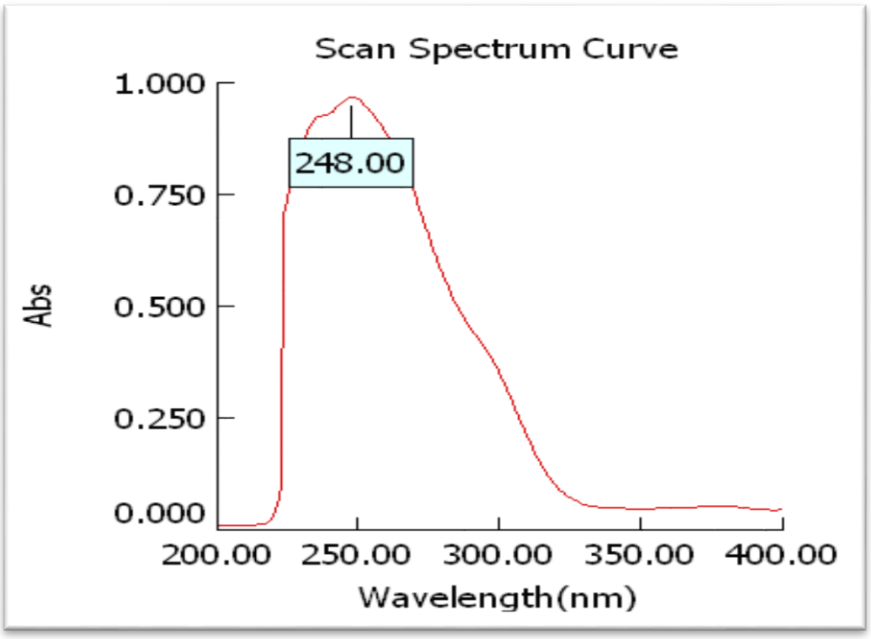


Figure 5. Determination of λ_{max} of Cinnarizine

Calibration Curve of Cinnarizine in 0.1N HCl

Following the absorbance of cinnarizine drug in different concentration in 0.1N HCl which was calculated:

Table 3. Calibration curve of cinnarizine in 0.1N HCl

S. No.	Concentration (µg/ml)	Absorbance (nm)
1	5	0.140
2	10	0.295
3	15	0.460
4	20	0.635
5	25	0.815

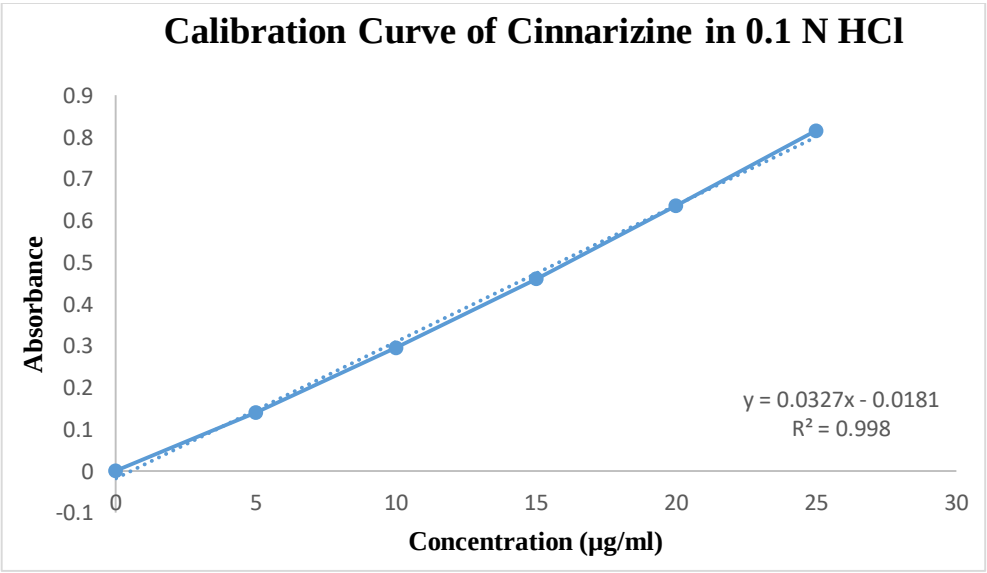


Figure 6. Linear reversion analysis for slandered curve

The linear reversion analysis was done on Absorbance data points. The results are as follow for standard curve

Slope = 0.032

The intercept = -0.018

The correlation coefficient (r^2) = 0.998

The calibration curve of cinnarizine was analyzed at 248nm in 0.1N HCl in a UV spectrophotometer. The slope, intercept, and the correlation coefficient was found and the calibration curve was plotted and the correlation coefficient (r^2) was 0.998.

Fourier-transform infrared spectroscopy (FTIR)

The IR spectrum of sample drug shows the peak values which are characteristics of the drug and the graph were shown in figure.

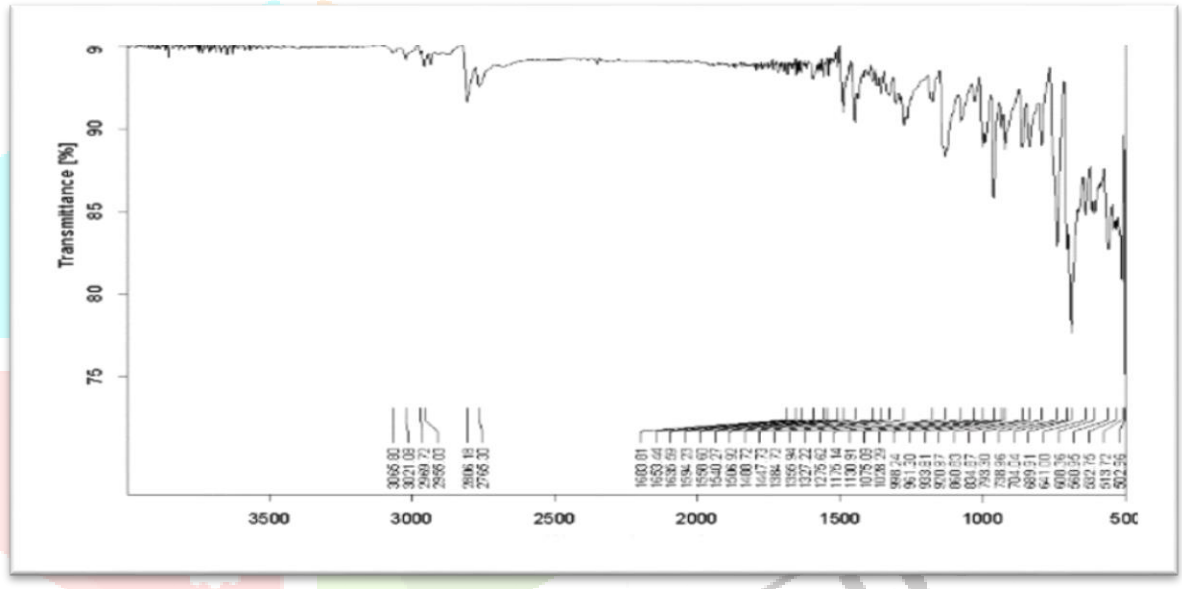


Figure 7. FT-IT spectrum of pure drug (cinnarizine)

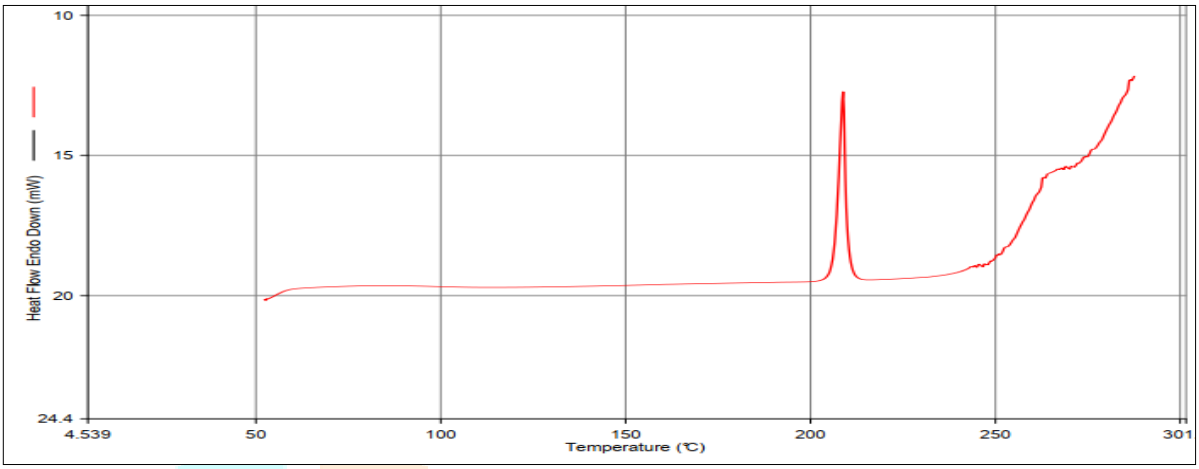
IR spectrum of compound (Cinnarizine) showed characteristic peaks at 2969, 2956 cm^{-1} (C-H str).

Table 4. Assignments of Cinnarizine

Frequency (cm-1)	Assignments
2969	C-H Stretching (aromatic, alkane)
2956	C-H stretch (aliphatic, alkane)
1594	C=C (aromatic stretch)
1488, 1447	CH_2 (alkane)
1130	C-N stretching
998,961	=C-H (out of plane) (aromatic, alkane)

FTIR shows the spectra for pure cinnarizine between the wavenumbers of 2969 cm^{-1} and 2956 cm^{-1}. The major absorption peaks obtained from this spectrum was given in Table 9.11 and these were identified with the functional groups that was responsible for the different modes of vibrations.

Drug–Excipient compatibility study (DSC)



DSC Thermogram of Cinnarizine

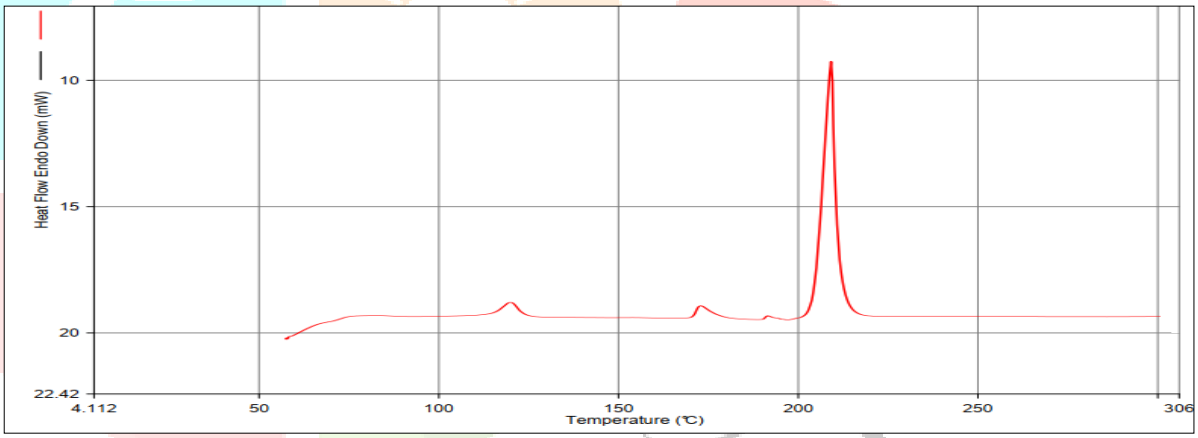


Figure 8. DSC Thermogram of Mixture of PVA and Cinnarizine

DSC thermogram of cinnarizine exhibited a melting point at 120^0C. The mixture of drug and excipients was kept in an accelerated condition of 40^0C/ 75% RH for 10 days and subjected to DSC analysis. The characteristic melting point of cinnarizine does not deviate from 120^0C that predicts that there is no interaction between drug and PVA.

EVALUATION OF 3D PRINTED TABLET

Weight Variation

The weight variation of all tablets is shown in the table. All the tablets are passed the weight variation test, all the tablet % weight variation was inside pharmacopeia limits of ±5% of the weight. The weight of the total tablet was found to be constant with low standard deviation values.

The weight variation of the 3D printed tablet was found to be 0.57%. According to Indian Pharmacopeia, our tablet weight variation was within the limit.

Friability

The value of the friability test was 0.095%. The % friability was less than 1% in the formulation confirming that the tablet was mechanically stable. Our 3D printed tablet friability was within the limit. That means our tablet was completely safe for transport.

Hardness

The hardness measured of the tablet of each batch between 6-7 kg/cm^2. According to Indian Pharmacopoeia, our tablet hardness was not under the limit. It was due to the plasticity nature of the PVA and hot melt too.

Drug Content

Drug Content of our 3D printed tablet was found to be 49.2 mg into 50 mg and % drug content was 98.4%. This result followed the acceptance criteria for drug content. It ensures that a consistent dose of the cinnarizine was maintained between batches so that the patient received the correct dose.

Table 5. Evaluation of 3D Printed Tablet

S. No.	% Weight Variation	% Friability	Hardness	% Drug Content
1	0.057%	0.095%	6,67 kg/cm^2	98.4%

***In-Vitro* Drug Release**

Following the cinnarizine loaded *In-vitro* drug release of 3D printed tablets which was calculated:

Table 6. *In-Vitro* Drug Release of 3D printed Tablet

S. No.	Time (Min.)	% Drug release
1	5	0.4±0.20
2	10	1.2±0.23
3	20	2.6±0.15
4	30	4.8±0.30
5	40	8.9±0.10
6	50	11.6±0.18
7	60	15.8±0.28
8	70	20.07±0.36
9	80	24.4±0.11
10	90	28.9±0.24
11	100	33.7±0.34
12	110	38.9±0.42
13	120	44.5±0.18
14	130	50.2±0.12
15	140	56.1±0.31
16	150	62.2±0.25
17	160	68.8±0.41
18	170	75.6±0.34
19	180	82.4±0.08
20	190	89.6±0.34
21	200	96.8±0.39

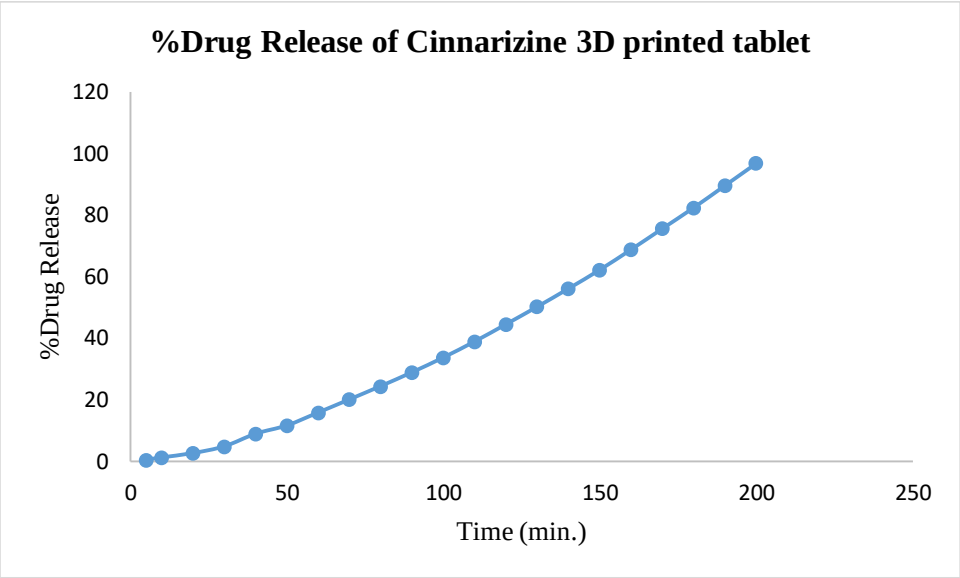


Figure 9. % Drug release of cinnarizine 3D printed tablet

The tablets were prepared by an FDM 3D printer using PVA as a polymer and cinnarizine as an API. Dissolution of the 3D printed tablet was done on the 0.1 N HCl because cinnarizine was soluble in an acidic medium. We calculate the cumulative drug release of all the tablets. All batches were shown similar drug release at 200 min. And % drug release of the tablet was found to be 96.8±0.39 at 200 min. This confirms that the FDM 3D printing process was capable of producing sustained-release tablets.

Release Kinetic Analysis

The kinetic values for the optimized formulations are shown in table no. 9.19 The values of *in vitro* drug release of Cinnarizine were attempted to fit into various mathematical models, such as zero order, first order, Higuchi matrix and Korsmeyer - Peppas model and it was shown that the developed batch followed zero-order drug release kinetics as the plots shows the highest linearity.

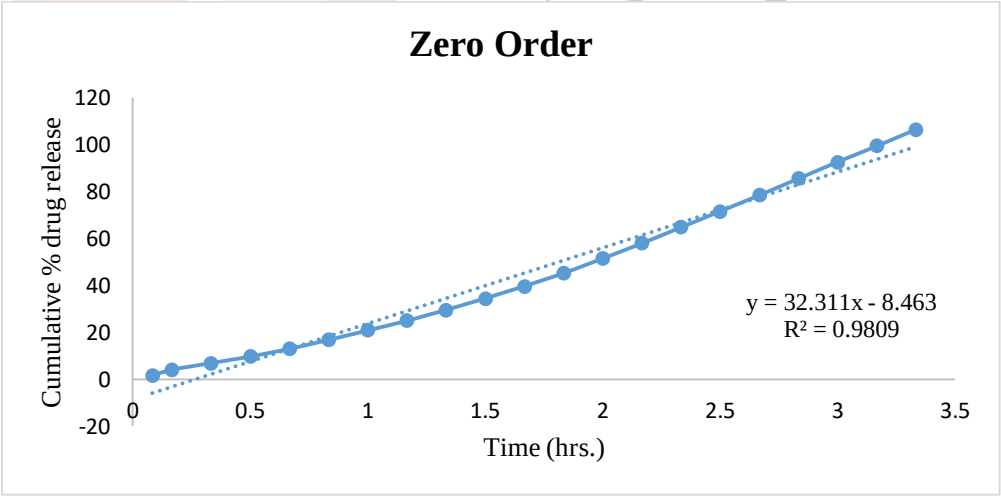


Figure 10. Graph between cumulative % drug released vs. time

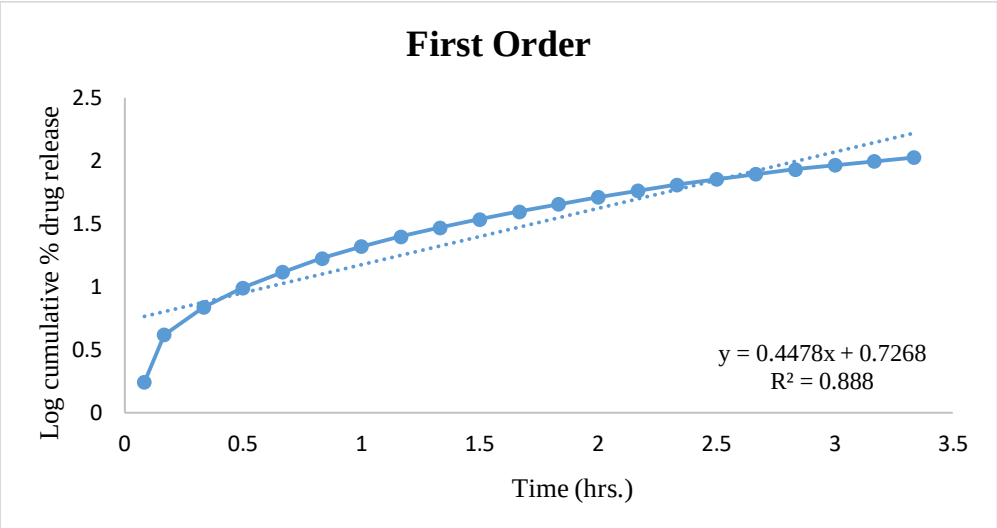


Figure 11. Graph between log cumulative % drug release vs. time

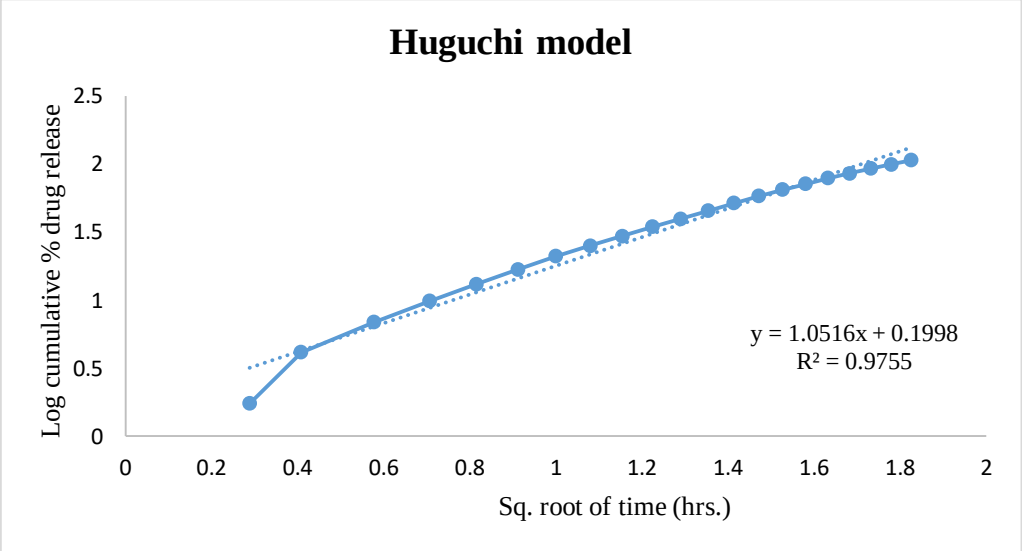


Figure 12. Graph between log cumulative % drug released vs. square root of time

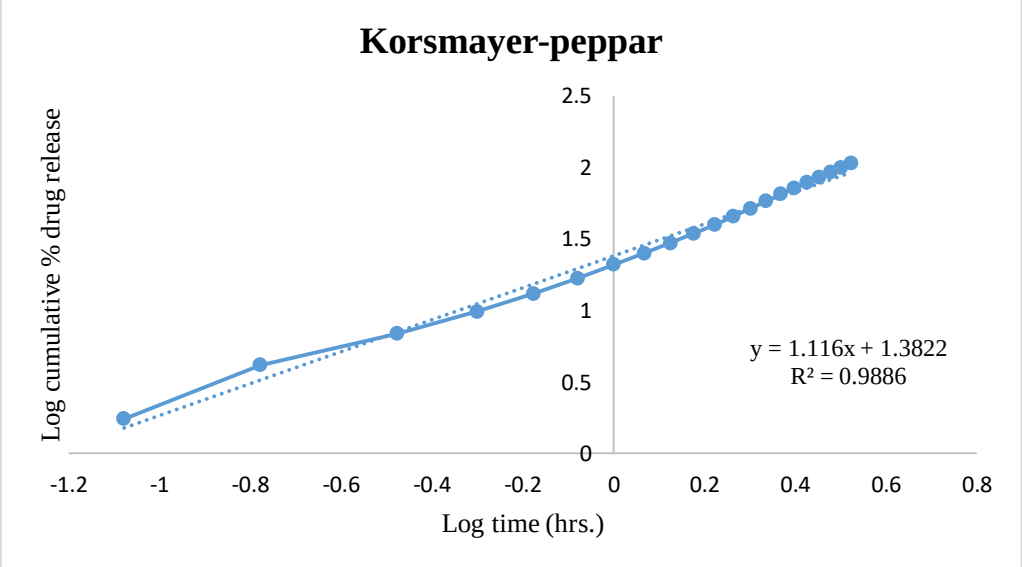


Figure 3. Graph between log cumulative % drug release vs. log time

Following the kinetic data of optimized 3D printed tablets which was calculated:

Table 7. Kinetic data of optimized 3D printed tablet

Formulation	Zero order	First order	Higuchi	Korsmeyer–peppar model	
3D printed tablet	R^2	R^2	R^2	R^2	N
	0.9807	0.888	0.9755	0.9886	0.812

To confirm the diffusion mechanism of cinnarizine from a 3D printed tablet, the dissolution data were subjected to the Korsmeyer and Peppas diffusion models. The 'n' value for the optimized formulation was found to be 0.812, indicating that the release mechanism was non Fickian or anomalous release ($0.45< n< 0.89$). It can beinferred that the release was dependent on both drug diffusion and polymer relaxation.

DISCUSSION

FDM 3D printing of PVA filament tablet with drug loading of Cinnarizine which is antihistamine category. The tablet was designed by AutoCAD then designed tablet was sliced by the Cura Ultimaker 4.4 software.

The preformulation study was conducted to determined different evaluation parameters like organoleptic evaluation, solubility, melting point, flow property, FTIR, and DSC of drug to identification and purity of drug. All results were within the acceptance range. Melting point of PVA was little higher than reported melting point. FTIR and DSC data shows that the cinnarizine form was unaffected by the printing and that there were no detectable interactions.

Cinnarizine was dissolved in acidic medium so that we used 0.1N HCl for dissolution. Drug was release from the tablet in same period of time respectively, effectively demonstrating sustain release. The 3D printing cinnarizine tablets were also evaluated for weight variation, hardness, friability, drug content, and tablet dimensions. All results were within acceptable range as defined by the Indian pharmacopoeia.

This work was validated that the FDM 3D printing process was capable for producing sustained release tablets. We believe this was a significant step forward in the potential extensive take up of 3D printing for the manufacture of medicines, particular in the areas of clinical development and personalized medicines. With this principal demonstrated, it becomes possible to envision control of drug release and dose (through dosage form size) on an individual basis using a 3D printer, without the need for forming complex mixtures from different formulation 'cartridges'

AKNOLEDGEMENT

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