Journal of Chemical Health Risks

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JCHR (2024) 14(3), 1530-1537 | ISSN:2251-6727

Formulation & Characterization of Sustained Release: Multichambered Tablet of Losartan Potassium Using Fused Deposition Modelling (FDM) 3D-Printer

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(Received: 04 February 2024 Revised: 11 March 2024 Accepted: 08 April 2024)

KEYWORDS
3D-Printing, Fused Deposition Modelling, Sustained Release, Additive Manufacturing, Poly vinyl Alcohol (PVA), Rapid prototyping

ABSTRACT:

Introduction: The Aim of present research work was to formulate and characterize Sustained release: Multichambered Tablet Using Fused Deposition Modelling (FDM) 3D-Printer, the drug candidate used in this project was Losartan Potassium, is an Angiotensin receptor Type -II blocker.

Objectives: By altering the shell thickness and infill density %, sustained release action of tablet using API Losartan Potassium had been achieved.

Methods: The Novel method had been used for fabricating Tablet called "Pause and fill Method". Tablets was prepared using FDM 3D-printer with three different batches (FI, FII and FIII) by creating variation in infill-density and inner wall thickness: 0.5mm, 1mm and 1.5 mm respectively using poly vinyl alcohol (PVA) filament. As half-life of Losartan is 1.5–2hrs (Indian Pharmacopoeia, 2018) with poor bioavailability, sustained release tablet enhanced the bioavailability of the drug, the *in-vitro* drug release from the tablet drug is extended upto 270mins (approx.).

Results: From the Results it concluded that the FIII batch of tablet is the optimized batch with drug release about 99.23 % for 270 mins, whereas FII shows 98.69 % for 240 mins and FI shows 97.71% for 210 mins. The data when used to evaluate the kinetic studies, states that the coefficient 'r' indicated the drug release from the tablet which was followed by zero order release kinetics.

Conclusions: The work conclude that the FDM 3D printing process was capable for producing rapid and sustained release tablets on the basis of different thickness. This work also helps to decrease the side effects of drugs by providing sustained release of drugs & increase the safety and efficacy and avoid incompatible between APIs by developing drug release characteristics. The printer software enabled easy fabrication of oral drug delivery devices with different wall or chamber thickness.

1. Introduction

Novel Drug delivery systems are the techniques which are day by day getting more developed and more accurate for delivering of therapeutic doses, which are tailored according to the patient need or requirement. Additive manufacturing technology includes various types of 3D-printing methods are as follows: Stereolithography (SLA), selective laser sintering (SLS), inkjet-based 3D-printing and Fused deposition modelling (FDM). Such novel methods can be used in choosing the doses i.e, flexibility in selection of amount of drug or API, shape and size of the dosage, etc [1–3] A Rapid proto-typing technology, due to it's cheapest printing costs, high printing quality, and well capacity to employ drug-loaded filaments via hot-melt extrusion (HME), Fused deposition modelling (FDM) is one of the additive

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JCHR (2024) 14(3), 1530-1537 | ISSN:2251-6727

manufacturing techniques that is most oftenly researched or used for formulating dosage forms, or even in case of bioprinting in medical emergencies [4,5].

The "three Ds of 3D printing" refers to the overall procedure of 3D-printing method. These are (i) Design, (ii) Development and (iii) Dispense. This technique is only now beginning to be adopted by the pharmaceutical sector. There aren't any significant companies in the pharmaceutical sector creating drugs for regular use. Chuck Hull's stereolithography apparatus (SLA) received the first patent in 1986, which is when 3D printing initially emerged. He is regarded as the originator of 3D printing technology as well printing in the biomedical and pharmaceutical industries or field had been introduced in the year of 2015 [6–8]. Numerous firms are investigating this possibility, including Teva and Aprecia Pharmaceuticals. A high medication load, up to 1,000 mg, may be delivered in a single dosage thanks to ZipDose Technology. By administering even the highest concentrations of levetiracetam with only a sip of drink, “SPRITAM” was authorized by the US Food and Drug Administration (FDA) on year August 3, 2015, to treat partial-onset, myoclonic, and generalized tonic-clonic seizures improves the patient experience. Using 3DP technology, which was developed at Massachusetts Institute of Technology, Aprecia created its ZipDose Technology platform [9–11]

An appropriate polymer is chosen, melted, and then pushed or introduced through a heated nozzle out that may be moved. The polymer is applied layer by layer along all three following axis i.e, (x, y, and z axis), and when it get solidified, it takes on the precise shape as per the computer-aided design (CAD) models had intended into machine [12–14]. The invention and experiments using 3D -printing method had been described illustratively in **Figure 1**

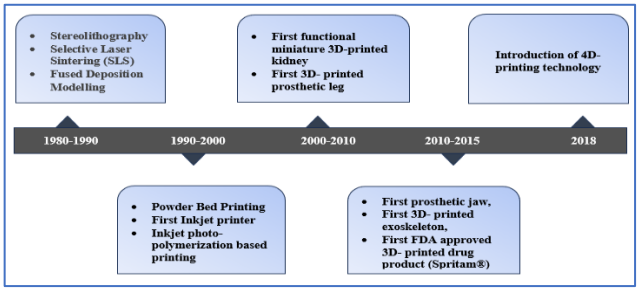

Figure 1: Inventions & Experiments using 3D-Printing

2. Objectives

The aim of this research work is that the FDM 3D printing process was capable for producing rapid and sustained release tablets on the basis of different thickness. This work also helps to decrease the side effects of drugs by providing sustained release of drugs & increase the safety and efficacy and avoid incompatible between APIs by developing drug release characteristics. The printer software enabled easy fabrication of oral drug delivery devices with different wall or chamber thickness. DSC and HPLC are carried to check the identification and purity of drug. All results are within the acceptance range. DSC data showed that the Losartan Potassium drug was unaffected by the printing and that there were no detectable interactions. PVA compartments are designed by the use of CAD software (Auto-CAD) in two steps. First printing of the tablet upto 75% and then paused, again after the API filling manually the rest part of the body building up. PVA reservoir were fabricated in three different batches on the basis of different thickness of inner most walls and difference in infill densities (FI, FII, FIII).

The 3D printed tablets were evaluated for Size and shape, hardness, weight variation, dye test and drug release test. All results are within acceptable range as defined by Indian Pharmacopoeia. In drug release performance we found the best result from FIII batch because it showed up for longest period of time amongst the three batches of formulation i.e, sustained release action upto 270 mins (approx.) In this system the drug resent in the outer compartment or chamber with thin wall is released first and release of the drug in the thick layer of compartment only commences when the thin lay er is practically dissolved. Drug release kinetic data of the 3D printed (FIII) batch of tablet analyzed and found to be fitted into zero order drug release kinetics. First order, Higuchi and korsmeyer-peppas model. Almost all formulations were well fitted in zero-order drug release kinetics with the highest linearity

3. Methods

Model Designing of 3D- Tablet

The tablet model had been designed using CAD software (Auto-CAD), then the STL file is further sliced using Cura-Ultimaker and converted into G-code format file i.e, Machine readable format. The filament which was used

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for the fabrication of the sustained release multi-chambered tablets namely Poly-vinyl Alcohol (PVA) filament. PVA is a water- soluble, biodegradable Polymer which is widely used by the researchers in the preparation or fabrication of the Pharmaceutical Formulation using 3D- Printer, due to its flexibility and physiochemical properties. **Figure 2** provides brief working of 3D- printing process[15].

This section outlines plan and how the process had been carried out. In this study "Pause and fill method". The structure was printed by a single-nozzled (0.4 mm in diameter) FDM 3D printer (3D-Prototyperz, DEX 200, Indore, India). The filament which is used to fabricate the Tablet is Poly vinyl alcohol (PVA) which is a water-soluble and biodegradable polymer. This Tablet is having 2 hollow chambers in which the drug (API) is to be filled shown in **Figure 3** The outer most chamber wall is having thickness of 1.5mm and the inner-most wall thickness is about 1.0 mm. The command had been given to the 3D-Printer using SD card in which the design of the tablet is saved in the format of g-code. The g-code file must be containing the command of stop i.e; after the completion of 75-80 % of the printing of tablet the machine will automatically be paused and then the desired dose will be poured into the different cavities or chambers of the tablet as per the need, then again just "press" print again and the remaining portion of the tablet will be printed successfully.

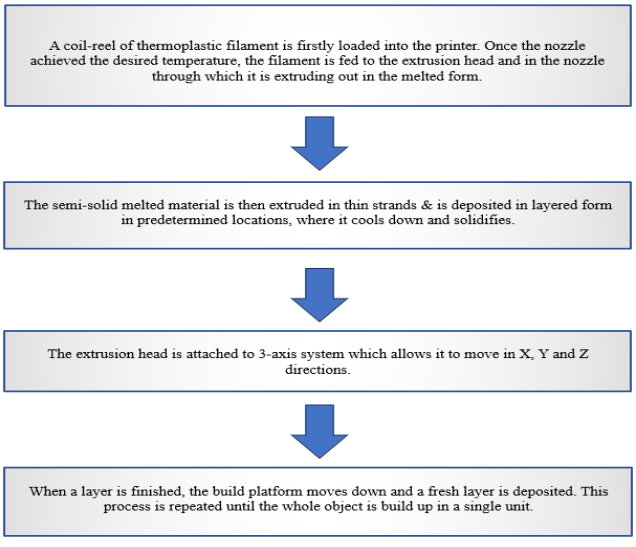

Figure 2: Flow chart showing processing of 3D-Printing of object

The printer parameter was adjusted by the 3D slicing software namely "Auto-CAD software" are as follows: a layer height of 0.1 mm, printing speed 10 mm/sec., infill density of 40%, 75% and 100% (FI, FII, FIII) respectively. The nozzle temperature were set to be at temperature 210 ˚C and the bed or printer tray temperature at 60 ˚C [16,17].

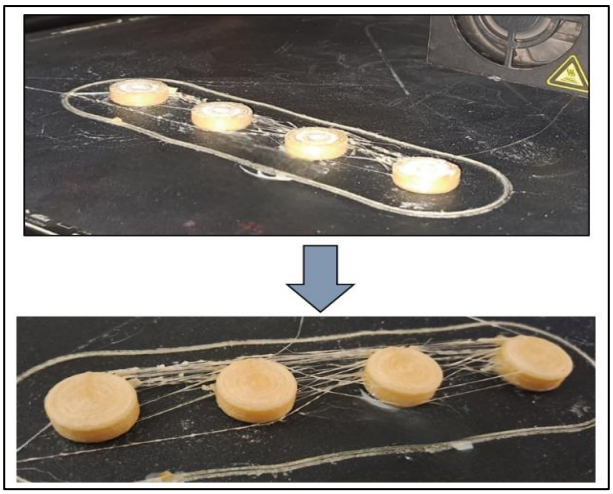

Figure 3: Printing procession of Tablet (After completion of 75% the nozzle is moved back, for the filling of the API)

4. Results

Losartan Potassium loaded Sustained Release: Multi-chambered Tablet were prepared successfully using Fused Deposition Modelling 3D- Printing method. The three batches of tablets had been prepared with different infill densities and inner-wall thickness, FI, FII and FIII with 40%, 75% and 100% infill density respectively. And the results were evaluated and observed as follows –

Size, Height, mass, width:

The shape of the tablet fabricated was circular containing chambers or cavities in the form of different layers vertically. The Diameter of the tablet was found to be 13 mm and height 0.5 mm. Three batches of the formulation were formulated i.e, FI, FII and FIII with different infill densities are as followed – 40%, 75% and 100% enlisted in **Table no. 1**

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JCHR (2024) 14(3), 1530-1537 | ISSN:2251-6727

Table 1: Size and shape of 3D- Printed tablets

S. No.	Diameter (mm)	Height (mm)	Infill density (%)	Inner chamber wall thickness (mm)
1.	13mm	5mm	40	0.5 mm
2.	13mm	5mm	75	1 mm
3.	13mm	5mm	100	1.5 mm

The thickness and the difference in the infill density of the tablet so the weight of the tablet found to be consequently increasing i.e, FI – 0.11% < FII – 0.27% <FIII – 0.39%. All the tablet batches were passed the weight variation test and within the acceptable limit (less than ±5 %) according to USP weight variation limit.

Differential scanning calorimeter (DSC)

DSC study was carried out to check the compatibility between Losartan Potassium and PVA filament used in the formulation. It is carried out to confirm that there should be complete physical compatibility of drug and filament with no mutual interaction. DSC thermogram of Losartan Potassium exhibited an endothermic peak at 278 ˚C followed by **Figure 4**

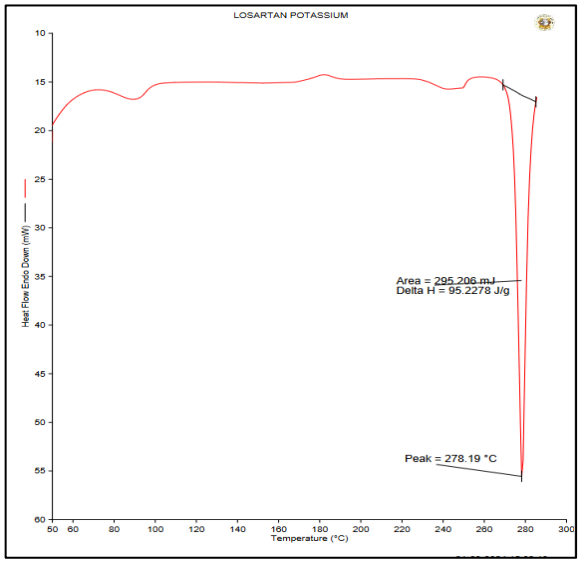

Figure 4: DSC report of Losartan Potassium

Whereas, the mixture of drug (Losartan) and polymer (PVA filament) was kept in an accelerated condition of 40 ˚C/ 75% RH for 10 days and subjected to DSC analysis. The mixture exhibits endothermic peak which was found approx. 275.34 ˚C, which suggested clearly that there was no interaction between Losartan Potassium and PVA filament and the drug Losartan Potassium was existed in it's unchanged form **Figure 5**

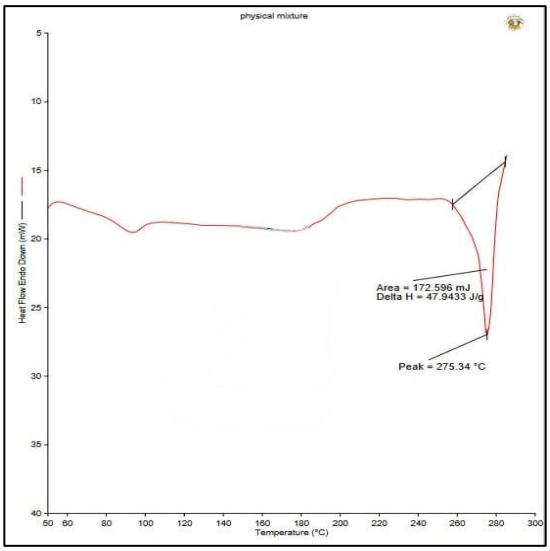

Figure 5: DSC report of mixture of PVA and Losartan Potassium

High Performance Liquid Chromatography (HPLC)

The chromatographic separation was performed using C_{18} column (250mm x 4.6mm x 5.0µm) including a Rheodyne injector with 10 µl fixed loop. Empower software had been used for the data analysis and interpretation. The mobile phase consists of 2 solvents: 0.1% Ortho-phosphoric acid (OPA) considered as mobile phase (A) and Acetonitrile (ACN) as, mobile phase (B) in ratios 75:25, 10:90, 75:25, 75:25 followed by I.P, 2018 edition. Run time of the method was set at 55 mins. The flow rate of the sample was 1ml/min. The readings are – *ref.* **Table 2 and Figure 6 & 7**

Table 2: - HPLC report conc./area

S. No.	Concentration (ppm)	Area (AUC)
1.	10	413061
2.	20	760424
3.	30	1129993

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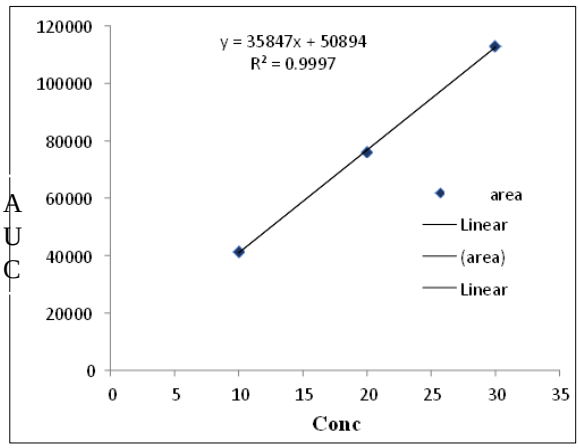

Figure 6: Graph of Losartan Potassium showing linearity Conc. (ppm)/AUC

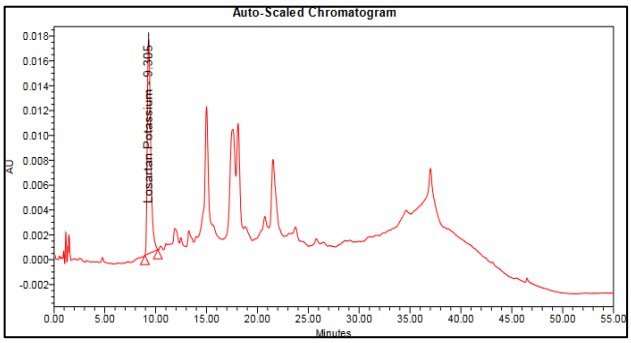

Figure 7: HPLC spectrum of Losartan potassium

Hardness Determination

The hardness measured of the tablet of each batch between 5-6.5 kg/cm^2. According to Indian pharmacopoeia 5.5±0.06 and 7.5±0.06 kg/cm^2 is the hardness limit of the matrix tablet which depicts good mechanical strength of tablet. It was due to the plasticity nature of the PVA. Hardness of the 3D- Printed Tablet is shown in **Table no- 3**

Table 3: - Hardness of 3D- Printed tablets (n=3)

Formulation	Hardness (kg/cm^2)			Average Hardness (kg/cm^2)
FI	5.8	6.2	5.9	5.9 ±0.61
FII	6.0	5.5	6.2	5.9 ±0.13
FIII	5.5	6.5	6.4	6.1 ±0.33

Dye Test

The results of Dye test reveals that the methyl orange starts releasing between 30 mins to 120 mins i.e, The outer chamber wall started dissolving between 30-120mins. whereas, inner chambers wall start dissolving and the methylene blue start releasing between 180 mins. to 270 mins. as shown in **Figure 8**

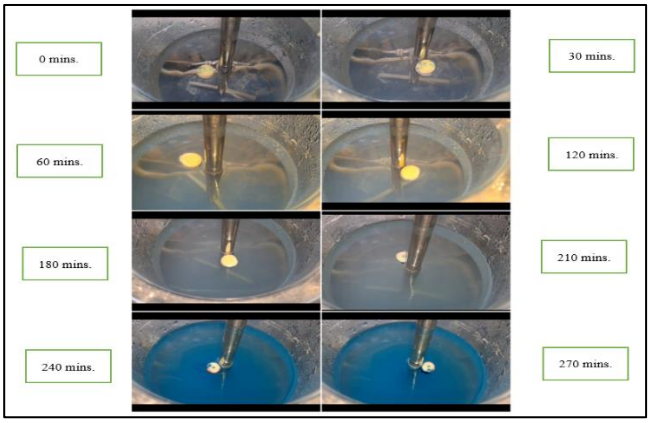

Figure 8: Photographs of dye test

***In-vitro* Drug release**

Dissolution study had been carried out at 0.1 N HCl medium at 205nm by maintaining the temperature about 37 ˚C ± 0.5 ˚C of the medium to mimic human stomach environment for all the three batches of tablet and the results clearly shows that the drug percentage release profile of the batch three i.e, FIII with infill density 100% and inner chamber wall thickness upto 1.5mm is having extended time duration and better drug release profile comparatively to the other two batches (FI and FII) of formulations shown in **Figure 9-**

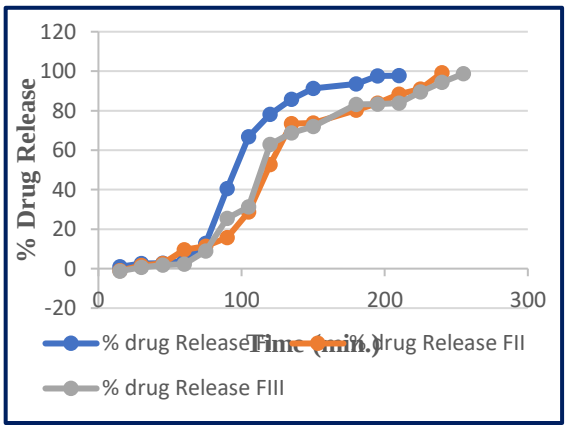

Figure 9: Percentage Drug release of 3D- Printed Tablet

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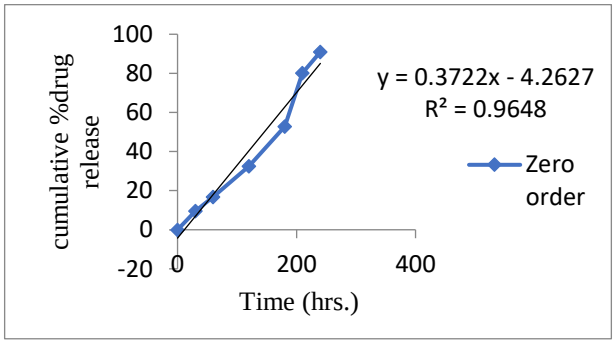
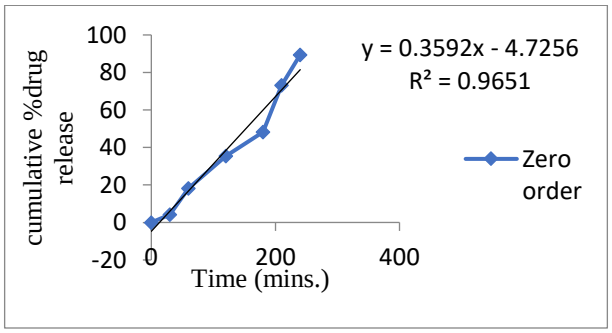
Drug release kinetics mechanism study

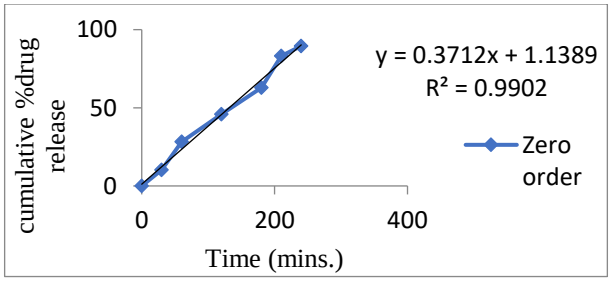
The kinetics of *in-vitro* drug release was calculated by applying the data of drug released to various kinetic model such as Zero order, First order, Higuchi and Korsmeyer – peppas. And the result obtained is shown in **Table 4**. From the results of kinetic studies, the coefficient 'r' indicated that the drug release followed zero order release kinetics. It was found that the value of 'r' for zero order ranged from 0.9651 to 0.9902, which is near to 1 when compared to first order ranged from 0.8089 to 0.9123. So, it was understood to be following zero order release pattern followed by all three formulations shown in **Figure 10** and **11**-



(a)



(b)



(c)

Figure 10: Graph between cumulative % drug release v/s time of Losartan Potassium (a) Formulation -I, (b) Formulation – II, (c) Formulation – III

Table 4: - Kinetic data of 3D- printed Tablet

Formulation	Zero order (r^2)
FI (40 %)	0.9648
FII (75%)	0.9651
FIII (100%)	0.9902

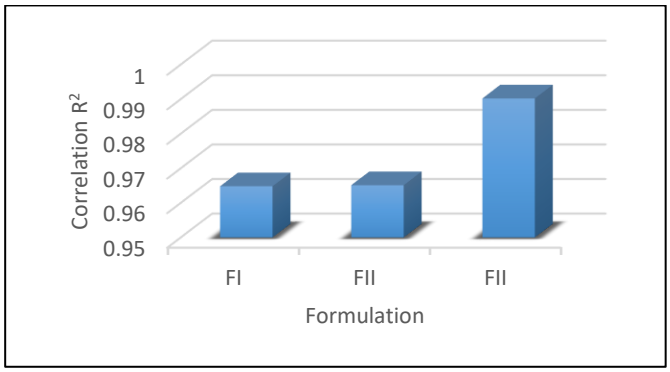


Figure 11: Chart showing the increase in R^2 value of zero order for all batches of formulation

5. Discussion

In conventional dosage form drugs, which are Amorphous nature, flocculent and low-density character is difficult to compress into a tablet. Hygroscopic drugs are not suitable for compressed tablets. Some limitations and problems like poor patient compliance, dose variation etc. Conventional dosage form has drawbacks like poor bioavailability and fluctuations in plasma drug level and are unable to achieve sustained release. Conventional oral dosage forms such as tablets or capsules undergo many production steps eg, granulation, compaction, size reduction, tableting or coating. In other hand, 3D printing reduces production to one or two steps, depending if there is pharmaceutical material in filament from available. 3D printing can revolutionize the world. 3D printing used to modify medicines as per the patient requirement involving the potentially to select optimal dose, appearances and release profile. Fused deposition modelling (FDM) is one of the most widely used 3D printing techniques to make solid dosages and offers accurate dosage by adjusting the parameters in CAD.

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JCHR (2024) 14(3), 1530-1537 | ISSN:2251-6727

This paper aim was to formulate and evaluate 3D printed Sustained Release: Multi-chambered Tablet using Fused Deposition Modelling (FDM) technology. The 3D printer uses a fixed amount of drug and polymer to print which minimizes the dose variation of the drug. Result accurate and precision dosing of the drug to the patients. Keeping in view of the above benefits, our aim was to explore 3D printing technology for formulation suitable dosage form of drug which may lead to reduce the dosing frequency, manufacturing cost and increase the patient compliance.

6. Acknowledgement

I would like to express my special gratitude to IOL Chemicals & Pharmaceuticals Ltd. (Ludhiana, Punjab, India) their valuable contributions, for providing Drug Gift sample of Losartan Potassium for this research. I also extend my appreciation to Nimita Manocha and Nadeem Farooqui, for their constant support and guidance. Their expertise and support were instrumental in the successful completion of this study.

References

1. Beg, S.; Almalki, W. H.; Malik, A.; Farhan, M.; Aatif, M.; Rahman, Z.; Alruwaili, N. K.; Alrobaian, M.; Tarique, M.; Rahman, M. 3D Printing for Drug Delivery and Biomedical Applications. *Drug Discovery Today* **2020**, *25* (9), 1668–1681.
2. Lee, T. C.; Shahrubudin, N.; Ramlan, R. An Overview on 3D Printing Technology: Technological, Materials, and Applications. *Procedia Manufacturing* **2019**, *35*, 1286–1296.
3. Mandloi, N.; Vinchurkar, K.; Mishra, D. K.; Dixit, P. 3D Printing for Drug Delivery and Its Pharmaceutical Applications – Recent Findings and Challenges. *PCI-Approved-IJPSN* **2022**, *15* (2), 5922–5931.
4. Mathew, E.; Pitzanti, G.; Larrañeta, E.; Lamprou, D. A. 3D Printing of Pharmaceuticals and Drug Delivery Devices. *Pharmaceutics* **2020**, *12* (3), 266.
5. Wang, S.; Chen, X.; Han, X.; Hong, X.; Li, X.; Zhang, H.; Li, M.; Wang, Z.; Zheng, A. A Review of 3D Printing Technology in Pharmaceutics: Technology and Applications, Now and Future. *Pharmaceutics* **2023**, *15* (2), 416.
6. Bhattacharya, S.; Singh, S.; Shrestha, S.; Baghel, Y. Recent Findings and Development of 3D Printing Technology in Pharmaceutical Formulation Development: An Extensive Review. *International Journal of Drug Development and Research* **2019**, *Volume 11, Issue 4* (2019), Volume 11(4): 1-14 (2019)-01-Volume 11(4): 1-14 (2019)-14.
7. Jamróz, W.; Szafraniec, J.; Kurek, M.; Jachowicz, R. 3D Printing in Pharmaceutical and Medical Applications – Recent Achievements and Challenges. *Pharm Res* **2018**, *35* (9), 176.
8. O Oyewumi, M. 3D Printing Technology in Pharmaceutical Drug Delivery: Prospects and Challenges. *J Biomol Res Ther* **2015**, *04* (04).
9. Chakka, L. R. J.; Chede, S. 3D Printing of Pharmaceuticals for Disease Treatment. *Front. Med. Technol.* **2023**, *4*, 1040052.
10. Jose, P. A.; Christoper GV, P. 3D PRINTING OF PHARMACEUTICALS – A POTENTIAL TECHNOLOGY IN DEVELOPING PERSONALIZED MEDICINE. *Asian Journal of Pharmaceutical and Development* **2018**, No. 2018;6 (3):46-54, 46–54.
11. Kun, K. Reconstruction and Development of a 3D Printer Using FDM Technology. *Procedia Engineering* **2016**, *149*, 203–211.
12. Abaci, A.; Gedeon, C.; Kuna, A.; Guvendiren, M. Additive Manufacturing of Oral Tablets: Technologies, Materials and Printed Tablets. *Pharmaceutics* **2021**, *13* (2), 156.
13. Ali, A.; Ahmad, U.; Akhtar, J. 3D Printing in Pharmaceutical Sector: An Overview. In *Pharmaceutical Formulation Design - Recent Practices*; Ahmad, U., Akhtar, J., Eds.; IntechOpen, 2020.
14. Jandyal, A.; Chaturvedi, I.; Wazir, I.; Raina, A.; Ul Haq, M. I. 3D Printing – A Review of Processes, Materials and Applications in Industry 4.0. *Sustainable Operations and Computers* **2022**, *3*, 33–42.
15. Maroni, A.; Melocchi, A.; Parietti, F.; Foppoli, A.; Zema, L.; Gazzaniga, A. 3D Printed Multi-Compartment Capsular Devices for Two-Pulse Oral Drug Delivery. *Journal of Controlled Release* **2017**, *268*, 10–18.
16. Skowyra, J.; Pietrzak, K.; Alhnan, M. A. Fabrication of Extended-Release Patient-Tailored Prednisolone Tablets via Fused Deposition Modelling (FDM) 3D Printing. *European Journal of Pharmaceutical Sciences* **2015**, *68*, 11–17.

Journal of Chemical Health Risks

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17. Goyanes, A.; Chang, H.; Sedough, D.; Hatton, G. B.; Wang, J.; Buanz, A.; Gaisford, S.; Basit, A. W. Fabrication of Controlled-Release Budesonide Tablets via Desktop (FDM) 3D Printing. *International Journal of Pharmaceutics* **2015**, *496* (2), 414–420.
18. Al-Majed, A.-R. A.; Assiri, E.; Khalil, N. Y.; Abdel-Aziz, H. A. Losartan. In *Profiles of Drug Substances, Excipients and Related Methodology*; Elsevier, 2015; Vol. 40, pp 159–194.
19. Patel, N. G.; Serajuddin, A. T. M. Development of FDM 3D-Printed Tablets with Rapid Drug Release, High Drug-Polymer Miscibility and Reduced Printing Temperature by Applying the Acid-Base Supersolubilization (ABS) Principle. *International Journal of Pharmaceutics* **2021**, *600*, 120524.
20. Zhao, X.; Wei, W.; Niu, R.; Li, Q.; Hu, C.; Jiang, S. 3D Printed Intragastric Floating and Sustained-Release Tablets with Air Chambers. *Journal of Pharmaceutical Sciences* **2022**, *111* (1), 116–123.
21. Qian, H.; Chen, D.; Xu, X.; Li, R.; Yan, G.; Fan, T. FDM 3D-Printed Sustained-Release Gastric-Floating Verapamil Hydrochloride Formulations with Cylinder, Capsule and Hemisphere Shapes, and Low Infill Percentage. *Pharmaceutics* **2022**, *14* (2), 281.