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Exploring Feasibility Of Placebo Oral Formulation By Conventional And 3D Printing Method

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Abstract:

Extrusion-based 3D printing technology represents a promising and relatively recent method with the potential to revolutionize the fabrication of pharmaceutical products across various dosage forms. Its distinct advantages over traditional manufacturing methods include enhanced precision in drug dosing, a critical factor for drugs requiring meticulous customization, such as those with a narrow therapeutic index. In this study, we successfully employed a syringe extrusion 3D printing technique to produce orodispersible films (ODFs) and compare their characteristics with those fabricated through the solvent-casting method. Different film-forming polymers like Polyvinyl Alcohol, Methocel and HPMC, PEG 4000, PEG 6000 & glycerin, and propylene glycol functioned as plasticizers. feasibility trials of film in 3d printer and by conventional method were performed. Mouth dissolving film was prepared successfully by 3D printing by pressure-assisted micro syringe method using HPMC K15 M and HPMC K100 M as polymer, Sucralose as sweetener, Citric Acid as saliva stimulating agent, PEG 400 and Glycerine as plasticizer, IPA and Water as solvent. So it can be concluded that mouth-dissolving film in both conventional methods and 3D Printing Methods. Formula by 3D printer by using a pressure-assisted micro syringe is ready for further trials with drug loading.

Keywords: 3D printing; syringe extrusion 3D printing; hydroxypropyl methylcellulose; orodispersiblefilm

1. Introduction

Over the final few decades, there has been a developing intrigue within the utilization of three-dimensional (3D) printing innovation inside the medical and pharmaceutical fields to manufacture the customizable solid dosage forms that suit distinctive needs, preferences, and individual characteristics of each quiet [1]. Three-dimensional printing may be a fabricating strategy that can create 3D-printed items of any shape and estimate on request from advanced plan software through storing materials layer-by-layer [2]. This innovation includes three commonly utilized strategies: printing-based inkjet (IJ) systems, nozzle-based deposition frameworks or extrusion (solid or semi-solid)-based printing techniques, and laser-based composting systems. Among these, the extrusion-based printing method has been recognized as the foremost well-known popular strategy for the creation of solid oral dosage forms owing to their fabulous capability to print with a more extensive choice of polymers and drugs at room temperature and the capability to join tall sums of drugs at low cost [1,3]. Various considerations have been performed concerning the benefits of extrusion-based 3D printing to plan different novel dosage forms such as polypills, gastro-floating tablets, and orodispersible films (ODFs).[4]. ODFs are a relatively novel dose frame arranged by utilizing hydrophilic polymers and designed to rapidly disintegrate within a minute within the buccal cavity, without requiring water [5]. This dose frame shows a few preferences over other oral dosage forms, including ease of administration to pediatric and geriatric patients encountering dysphagia (swallowing difficulty), dose flexibility, and moving forward the bioavailability of drugs due to high vascularity and tall permeability within the buccal cavity [6]. The major advantage of planning an ODF by 3D printing over the standard film solvent casting is the capacity to print objects with diverse filling (empty, matrix, or full), and the dosage of drugs can be controlled by calculating the material consumption during the resizing of the printed object at the design stage, which is appropriate for personalized treatment. Additionally, 3D-printed films can be formulated in less sum of time.

A assortment of hydrophilic polymers such as polyvinyl liquor (PVA), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), hydroxypropyl cellulose (HPC) and hydroxypropyl methylcellulose (HPMC) are utilized as film-forming polymers for the arrangement of ODFs, and most of them can moreover be utilized as printing materials for extrusion-based 3D printers [7,8]. Hydroxypropyl methylcellulose (HPMC), moreover known as hypromellose, is broadly implemented in pharmaceutical manufacturing as a binder, thickening agent, hydrophilic matrix material, and film-forming material. It is classified into a few grades based on viscosity, degree of hydroxypropyl substitution, and degree of methoxy substitution. The diverse consistency HPMC grades are frequently utilized for ODF arrangement and are appropriate for extrusion-based 3D printing of oral dosage forms.[8–10]. Additionally, the use of HPMC, which could be a hydrophilic polymer, can be further beneficial in terms of improving the solubility and disintegration of ineffectively water-soluble drugs within the manufacture of solid dispersion. In any case, there are still restricted thinks about accessible on the preparation of 3D-printed ODFs whereas using low-viscosity HPMC as a film-forming polymer. In the past study, levocetirizine dihydrochloride ODFs comprising HPMC E15 and pregelatinized starch were arranged to employ a semi-solid extrusion (SSE) 3D printer. The 3D-printed ODFs displayed great flexibility and quick drug release in vitro by dissolving totally in two minutes [11]. In expansion, past work on the extrusion-based 3D printing of HPMC within the pharmaceutical field can be found [12]. The extrusion-based (fused-deposition modeling) 3D printer was utilized to manufacture 3D-printed tablets by utilizing their developed HPMC filament.

Various approaches were employed to overcome the solubility problem of different drugs. One of the promising techniques for enhancing its solubility is the Solid dispersion of the drug in a hydrophilic polymer. There are many available dosage forms of drugs on the market, such as oral suspension, chewable tablets, capsules, and intravenous injections. The development of ODF has numerous advantages over conventional dosage forms such as convenience for patient administration, accurate drug dosing, rapid onset of action with increased bio-availability due to

bypassing hepatic first-pass effect and noninvasiveness. Moreover, ODF can be used for patients and can be taken without water due to its ability to disintegrate within a few minutes to release medication in the mouth.

2. Materials and Equipments

2.1. Materials

Table 1 List of materials

Sr. No.	Material	Function	Manufacturer
1.	Polyvinyl Alcohol	Polymer	Colorcon, India.
2.	Methocel E3	Polymer	Colorcon, India.
3.	Methocel E5	Polymer	Colorcon, India.
4.	Methocel E15	Polymer	Colorcon, India.
5.	HPMC K 15 M	Polymer	Colorcon, India.
6.	HPMC K100 M	Polymer	Colorcon, India.
7.	PEG 4000	Polymer	Colorcon, India.
8.	PEG 6000	Polymer	Colorcon, India.
9.	PEG 400	Plasticizer	Molychem, India
10.	Glycerol	Plasticizer	Molychem, India
11.	Sucralose	Sweetener	Firmeniech, Mumbai.
12.	Citric Acid	Saliva Stimulating Agent	Sudeep Pharma, Mumbai.
13.	Methanol	Solvent	Molychem
14.	Isopropyl alcohol	Solvent	Molychem
15.	Dichloromethane	Solvent	Molychem
16.	Acetone	Solvent	Molychem
17.	Chloroform	Solvent	Molychem

2.2. List of Equipments

Table 2 List of Equipments

Sr. No.	Equipments	Manufacturers
1	Digital weighing balance	Reptech weighing balance ltd., Ahmedabad.
2	Sonicater	Lava lab, India.
3	Dissolution apparatus	Electro lab ltd, Mumbai.
6	Magnetic stirrer	Janki Impex Pvt. Ltd, Ahmedabad.
7	pH Meter	Janki Impex Pvt. Ltd, Ahmedabad.
8	Vernier Calliper	Mitutoyo, Japan.
9	3D Printer	3 Fce Tech, Himmatnagar.

3. Experimental work

3.1. Placebo Trials for Selection of water soluble polymers

Initially, for the selection of suitable polymers, various film forming polymers such as HPMC Grades were chosen for further screening. PEG 400 was selected as a plasticizer, Citric acid as a saliva stimulation agent, and Sucralose as a sweetener. To dissolve the drug in less quantity of solvent, ethanol was selected as solvent. Following is the composition table for Feasibility batches.

Table 3 Selection of water soluble polymers

Ingredient / Patch (mg)	B1	B2	B3	B4	B5
Methocel E3 LV	100	–	–	–	–
Methocel E5 LV	–	100	–	–	–
Methocel E15 LV	–	–	100	–	–
PEG 4000	–	–	–	100	–
PEG 6000	–	–	–	–	100
Sucralose	5	5	5	5	5
Citric Acid	4	4	4	4	4
PEG 400 (ml)	0.2	0.2	0.2	0.2	0.2
Water (ml)	10	10	10	10	10

Table 4 Selection of water soluble polymers

Ingredient/Patch (mg)	B6	B7	B8	B9
PVA	100	–	–	–
HPMC K15 M	–	100	–	–
HPMC K100 M	–	–	100	–
HPMC K15 M + HPMC K100 M(1:1)	–	–	–	100
Sucralose	5	5	5	5
Citric Acid	4	4	4	4
PEG 400 (ml)	0.2	0.2	0.2	0.2
Water (ml)	10	10	10	10

3.2. Placebo Trials for Selection of Solvent

Table 3.1 Selection of Solvent

Ingredient/Patch (mg)	B10	B11	B12	B13	B14	B15
HPMC K15 M + HPMC K100 M (1:1)	100	100	100	100	100	100
Sucralose	5	5	5	5	5	5
Citric Acid	4	4	4	4	4	4
PEG 400 (ml)	0.2	0.2	0.2	0.2	0.2	0.2
Water (ml)	10	–	–	–	–	–
Methanol (ml)	–	10	–	–	–	–
IPA (ml)	–	–	10	–	–	–
DCM (ml)	–	–	–	10	–	–

Acetone (ml)	–	–	–	–	10	–
Chloroform (ml)	–	–	–	–	–	10

3.3. Placebo Trials for Selection of Solvent Ratio

Table 6 Selection of Solvent Ratio

Ingredient/Patch (mg)	B16	B17	B18	B19	B20	B21
HPMC K15 M + HPMC K100 M (1:1)	100	100	100	100	100	100
Sucralose	5	5	5	5	5	5
Citric Acid	4	4	4	4	4	4
PEG 400 (ml)	0.2	0.2	0.2	0.2	0.2	0.2
Water:IPA (1:1) ml	10	–	–	–	–	–
Methanol:DCM (1:1) (ml)	–	10	–	–	–	–
Acetone:Water (1:1) (ml)	–	–	10	–	–	–
Water:IPA (1:2) ml	–	–	–	10	–	–
Water:IPA (1:3) ml	–	–	–	–	10	–
Water:IPA (2:1) ml	–	–	–	–	–	10

3.4. Placebo Trials for Selection of Polymer Ratio

Table 7 Selection of Polymer Ratio

Ingredient/Patch (mg)	B22	B23	B24	B25
HPMC K15 M	150	50	175	125
HPMC K100 M	50	150	25	75
Sucralose	5	5	5	5
Citric Acid	4	4	4	4
PEG 400 (ml)	0.1	0.1	0.1	0.1
Glycerine (ml)	0.1	0.1	0.1	0.1
Water : IPA (1:3)	10	10	10	10

Table 8 Selection of Polymer Ratio

Ingredient/Patch (mg)	B26	B27	B28	B29
HPMC K15 M	240	200	160	180
HPMC K100 M	200	240	280	260
Sucralose	5	5	5	5

Citric Acid	4	4	4	4
PEG 400 (ml)	0.1	0.1	0.1	0.1
Glycerine (ml)	0.1	0.1	0.1	0.1
Water (ml)	3	3	3	3
IPA (ml)	7	7	7	7

4. Fabricationof3D-Printed Orodispersible Film

Feasibility Trials were initiated to identify suitable film-forming polymers for film preparation. Different water-soluble polymers used first like Methocel E3 LV, Methocel E5 LV, Methocel E15 LV, PEG 4000, PEG 6000, PVA, HPMC K15 M, HPMC K100 M, HPMC K15 M + HPMC K100 M (1:1). Combination of polymer showed good result after that at fix ratio taken and selection of solvent in singular and in combination batches were taken with Water, Methanol, IPA, DCM, Acetone, Chloroform, Water: IPA (1:1), Methanol: DCM (1:1), Acetone: Water (1:1), Water: IPA (1:2), Water: IPA (1:3), Water: IPA (2:1). Evaporation rate is competitively good of Water: IPA (1:3) combination so, that is fixed for formula. Afterward, the finalization of the polymer was done next. Batch B1 to B29 without drug loading has been done for the selection of polymers, solvents, plasticizers, solvent ratios, and polymer ratios. To prepare the printing dispersions for fabrication, the following steps were taken. First, the HPMC ratio was dispersed in specific proportions as listed in Table 3 to Table 8 in the different solvents and stirred in a magnetic stirrer for 2 minutes then put in a sonicater for 10 minutes at room temperature (25 ± 2 ◦C). Subsequently, the two different plasticizers (glycerin and propylene glycol 400) were added into the dispersions of 0.1 ml. The dispersions were sonicated for around 10 minutes at room temperature (25 ± 2 ◦C) gently until all of the air bubbles disappeared. The dispersion was loaded into a 10 mL disposable syringe attached with 21 G needle tips and then printed with the 3d printer's parameters. The total printing time was approximately 2 min for each film. After printing, the printed ODFs were placed at room temperature for 15–30 minutes to complete the drying process.

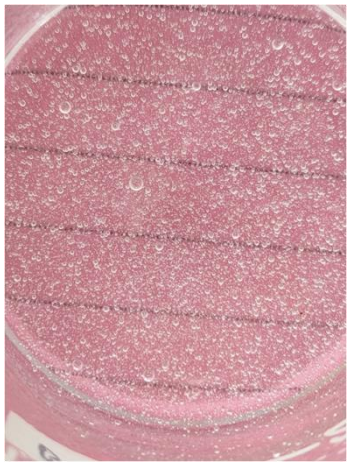

Figure 1 Initial Process of formulation

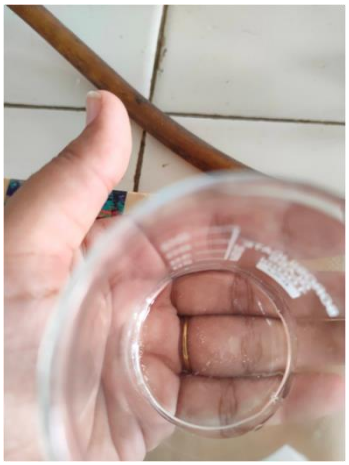

Figure 2 After sonication Process

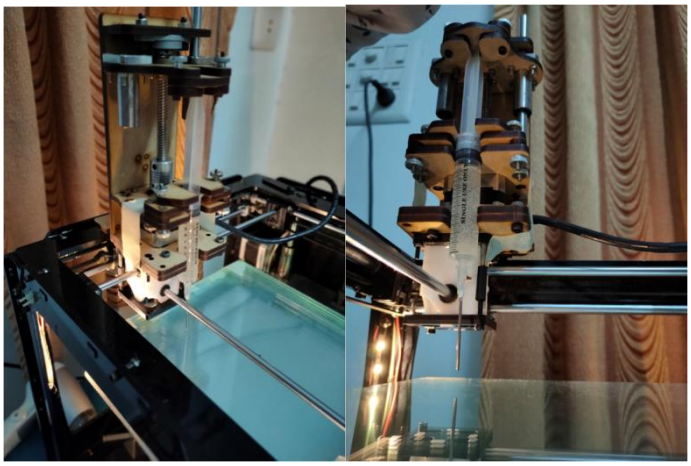

Figure 3 Semi-solid extruder(Pressure-assisted microsyringe) from two angle

Figure 4 Both pictures are 3D printed orodispersible film

5. 3D Printer,Design and Printing Parameters

In this study, the syringe extrusion 3D printer developed by the 3 Fce Tech was used to fabricate the 3D-printed ODFs.3D printer in which an extrusion nozzle can move in an X and Y axis and also on separate building plate on a Z-axis while printing layer-by-layer for 3D structure generation to prevent vibration on the sample, This customized syringe extrusion 3D printer is based on a core-XY. For précised deposition, a customized extruder was designed and built in-house which is syringe-based for the project. The syringe extrusion 3D printer was controlled by a laptop or system and a user interface on the printer. In Figure, the syringe-based extruder used a stepper motor to move a plunger of a 10 mL syringe via a direct lead screw drive. After an object is designed using

an open-source program and is divided into numerous two-dimensional (2D) layers can be called slices of design with a defined thickness, infill, and speed of printing in 3D printing. These 2D layers can be piled up with instruction of computer-aided design (CAD) models by selectively adding the desired materials in a highly repetitive manner layer-by-layer manner.

The 3D printing is done by using a syringe extrusion 3D printer. Initially, as shown in Figure, the 3D designs and models of the printed ODF with the dimension of 20 mm width × 20 mm length × 0.2 mm height were obtained by Tinkercad® software (2020, Autodesk Inc., San Rafael, CA, USA). By a simple constructive solid geometry method, the 3D models were constructed and exported as a 3D printer readable stereolithography (.stl) file format to Repetier-Host software. Then, the .stl file was sliced and converted to a 3D printable code (G-code) by the open-source software Slic3r. Then, the samples were transferred into a 10 mL disposable syringe (14.5 mm diameter), and the 3D models were printed with a syringe extrusion 3D printer equipped with a single-head printing extruder nozzle with a diameter of 0.51 mm (21 G). The printing process was conducted 10 mm/s printing speed and 120 mm/s at 25 ◦C nozzle traveling speed, and the printing parameters were preset as follows: the layer height was 0.2 mm, the fill angle was 45◦, the perimeters were 2, and the infill was defined as rectilinear with 100% ratio (For the measurement of the diameter of printed filaments, the infill was set as 0% of the volume, and the perimeter was 1).

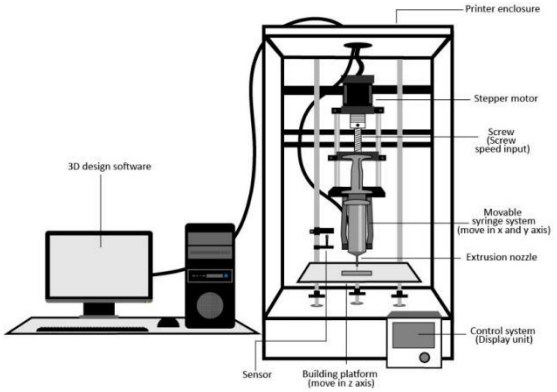

Figure 5 Schematic diagram of syringe extrusion 3D printer

6. Results & Discussion

Here are the Results of Feasibility Trials.

Table 9 Feasibility Trial Results

Batch	Conventional Method	3D Printing Method
B1	✓	✗
B2	✓	✗
B3	✓	✗
B4	✓	✗
B5	✓	✗
B6	✓	✗
B7	✓	✗
B8	✓	✗
B9	✓	✓

B10	✓	✗
B11	✓	✗
B12	✓	✗
B13	✓	✗
B14	✓	✗
B15	✓	✗
B16	✓	✓
B17	✓	✓
B18	✓	✓
B19	✓	✓
B20	✓	✓
B21	✓	✓
B22	✓	✓
B23	✓	✓
B24	✓	✓
B25	✓	✓
B26	✓	✓
B27	✓	✓
B28	✓	✓
B29	✓	✓

7. SUMMARY & CONCLUSION

- The best polymers and plasticizers were selected based on their preliminary evaluations. Mouth dissolving film was prepared successfully by 3D printing by pressure-assisted micro syringe method using HPMC K15 M and HPMC K100 M as polymer, Sucralose as sweetener, Citric Acid as saliva stimulating agent, PEG 400 and Glycerine as plasticizer, IPA and Water as solvent.
- All physical parameters evaluated were found to be satisfactory from which formulation B29 was selected as the best formulation. Feasibility Trials were initiated to identify suitable film-forming polymers for film preparation in both methods conventional and 3D Printing Methods.
- Batch B1 to B29 without drug loading has been done for the selection of polymers, solvents, Plasticizer, solvent ratio, and polymer ratio in both methods conventional and 3D Printing Methods.
- So it can be concluded that mouth-dissolving film in both methods conventional and 3D Printing Methods is formulated according to results and formulation B29 shows good results from by 3D printer by using a pressure-assisted micro syringe is ready for further trials with drug loading.

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