Journal of Pharmaceutical Research International

33(46B): 522-531, 2021; Article no.JPRI.73346
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

A Study Based on Controlled Drug Release by 3D Printed Aloe-Vera Bi-Layer Tablet

Anurag Verma[1*], Piyush Mittal[1], Milind S. Pande[1] and Neelanchal Trivedi[1]

[1]Department of Pharmacy, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i46B32971
Editor(s):
(1) Dr. Francisco Cruz-Sosa, Metropolitan Autonomous University, México.
Reviewers:
(1) Gaurav Jain, IES, India.
(2) Raj Kaushal, National Institute of Technology Hamirpur, India.
Complete Peer review History: https://www.sdiarticle4.com/review-history/73346

Original Research Article

Received 05 July 2021
Accepted 10 September 2021
Published 23 October 2021

ABSTRACT

Aloe-Vera or Aloe barbadensis (botanical name) is a plant with many medicinal properties and have great importance in Ayurveda. Its leaves are succulent, erect, forming a thick rosette. The internal translucent pulp of Aloe-Vera is bound to a waxy crust or cuticle, and its vascular tissues transport minerals as well as water from the soil. Aloe Vera is being used as a major skin rejuvenating product, although it has varied medicinal properties also. In the present study, an attempt to make a method to create bi-layer tablets of Aloe-Vera, utilizing 3D printing techniques is presented. The method created doesnt affect the integral functional characteristics of the tablet. The method here contains creating an immediate release and sustained release tablet for making the Aloe-Vera to be used directly by the person for its numerous health effects. The tablet is designed so to be consumed by vegans as well since it is completely herbal.

Keywords: Aloe-vera; bi-layer; 3d printer; immediate release; sustained release; tablet.

1. INTRODUCTION

Aloe-Vera / ghritkumari / gwarpatha/ Kumari/ or Aloe barbadensis (botanical name), is a plant with very less stem or without the stem that grows to 100- 60 centimeters in height, spreading through offset. Aloe-Vera is grown in several variants across India, including some that

**Corresponding author: E-mail: anuragvermaiftm@gmail.com;*

runs wild as on shores of Western and Southern India. It is one of the most omnipresent plants around the globe for skin care and skin care manufacturing products. An Aloe-Vera crop land can be seen in Fig. 1. For the preparation of different drugs, the internal portion of the leaf containing gel and latex is utilized. It is composed of vitamin B12, B6, B2, B1, A, niacine & folic acid. Aloe-Vera equipped medications are utilized for burning or sun-burns, and also for a number of dermis disorders such as acne, psoriasis, pruritus, eczema, etc. [1].

Australia, India, Europe, Japan, and USA are among main planting areas for Aloe-Vera. Uttarakhand, Rajasthan, Orissa, Assam, Nagaland, Manipur, Maharashtra, Madhya Pradesh, Kerala, Jharkhand, Haryana, Mizoram, Gujarat, Arunachal Pradesh, Andhra Pradesh, and Punjab are among the Indian states where it is grown [1]. Therere around 160 varieties of Aloe in the Liliacae genus. Aloe abyssinica, Aloe littoralis, Aloe indica, Aloe perfoliata, Aloe vulgaris, Aloe chinensis, and Aloe barbedensis have been the most widely cultivated variants and also have the highest medicinal benefit [1]. Aloe species, like Aloe-Vera, have a dense crust that protects the inner translucent pulp and a dense crust that protects the common green fleshy leaves. Vascular tissues inside the leaf pulp carry minerals & water from the roots to the stems, synthesized substances to the root, and latex for preservation along its leaf tip [2]. The amount of intercellular spaces vary according to the size of the leaf as well as the age of the plant [2].

Aloe-Vera leaves are succulent, erect, forming a thick rosette. The gel derived from the plants leaves can be used for many medicinal purposes. For the previous several years, Aloe-Vera have developed the focus of much scientific examinations on many reported therapeutic properties. Aloe-Vera is bitter, as per Ayurveda-sweet in taste, act as a coolant, and aids to clear the bowel. Ayurveda refers to Aloe-Vera as a rejuvenating tonic that encourages skin well-being and the metabolic function of a healthy liver. Aloe-Vera is also commonly used in herbal treatments, cosmetic preparations, and as a dietary supplement [3]. Aloe gel consists of soluble sugars, such as β-polysaccharides, glycoproteins, amino acids, vitamins, anthraquinones, and enzymes [4,5], amongst various organic-biomolecules, comprising antiviral, anticancer, wound healing, antifungal, antibacterial, anti-inflammatory, and other biological properties that have encouraged an upsurge in the industrial and commercial production [6].

Fig. 1. Cultivation of aloe-vera plant on a crop land

As an evolving technology, 3-Dimensional (3D) printing has been a subject of interest in the medical profession, especially in the administration of medication. FDM i.e. Fused Deposition Modelling is one of the many 3D printing processes available that serves the purpose [7,8,9], moreover, inkjet printing, selective laser sintering [10] are already been utilized effectively in personalized medicine and have showed tremendous promise [11]. The leading advanced manufacturing technology [12,13] applied to customized oral dosage forms has been fused deposition modelling 3D printing. Apart from its inexpensive cost, the technique may be utilized with a wide range of pharmaceutically acceptable polymers, including methacrylate [14], cellulose, and poly-lactic acid [15]. A pressure-backed micro-syringe printing technique to formulate levetiracetam immediate-release tablets was applied by Aita et al. In 95–120 seconds, most of the printed tablets were disintegrated completely. The tablets composed of semi-solid polyvinyl alcohol (PVA) and polyethylene glycol released the medication completely in less than 10 minutes, whereas those made of polyvinylpyrrolidone-vinyl acetate copolymer (PVP-VA) released the drug slightly slowly [16]. A 3D printing system by uniting FDM and injection volume filling to fabricate personalized extruded scaffolds trailed by the injection of liquid or semi-solid systems was developed by Linares et al [17]. The flexible printing technology was utilized to make tablets with numerous drug release profiles [18]. Various researches proven that 3D printed tablets through lower infill density possess faster drug release because of their higher surface area [19,20]. These studies proposed that 3D printing could be utilized to fabricate customized medicine through manipulating the infill density of a tablet.

The aim of this paper is to design successful tablets using a relatively inexpensive method consisting of a 3D printer without affecting the therapeutic properties of Aloe-Vera. By the sanction of the 1st 3-Dimensional print drug by the FDA (USA) in 2015, this technology of engineered drug was then used to advance the pharmaceutical industry business, which eventually boosts the healthcare sector. In the fields of electronics, aerospace, manufacturing, vehicles, dentistry, robotics, etc., the use of 3D printers is extremely abundant, but their full potential in the field of pharmacy is still to be discovered [21]. In the pharmaceutical industries, between the years 1993-2003, the boost of powdered tablets created using 3D printer led to the oral dosage forms. After that the industry is continuing to advance [22]. Around 1993-2003, the rise in powdered tablets manufactured utilizing 3D printers contributed to oral drug delivery systems in the pharmaceutical industry. Thereafter, the sector will strive to evolve.

1.1 Research Questions

- Can Aloe-Vera be used to make controlled release bi-layer tablets?

2. LITERATURE REVIEW

Aloe Vera is a most popular skin-care and medicinal plant. It helps in rejuvenating the skin, has anti-ageing properties, helps to treat acne and rosacea, helps moisturizes scalps & hairs, encourages the growth of hairs, avoids itches on scalps, decreases dandruff and repair the hairs, and supports skin purification & general nourishment [3,23]. Aloe-Vera has many medicinal properties too such as it also encourages breakdown and function of the liver, support the wellbeing of intestines and removes the lethal element. Apart from this, it has important properties related to womens health; it supports healthy menstrual flow in women and reduces stretch marks after pregnancy [3,23].

Aloe-Vera is natural, herbal, and possesses Ayurveda properties. For thousands of years, the medicinal properties of Aloe-Vera have been recognized, and many of the claimed biological activities have been verified by modern science. The hydrating qualities of Aloe-Vera gel are exceptional. That is because it is loaded with polysaccharides that give it a wax feel. The poly-saccharides are very water-loving (hydrophilic) and readily attach to water. On the other hand, its structure creates a protecting layer for the dermis that aids in its healing abilities. It also improves epidermis resistance and the skins ability to heal itself [24]. Aloe-Vera is a popular cosmetic component in several consumer skincare products and skincare industries. The herb is very soft on the skin and seems to have a minimal risk of developing asthma, irritation, or allergy symptoms. Its popular in after-sun skincare products cosmetics, as well as facial, hair, and body care. Aloe-Vera is also a well-known medical research herb, with several experiments on its structure and properties been undertaken [24].

Fig. 2. Showing Aloe-Vera powder [23]

Aloe-Vera has been used with many other drugs as excipients but in the present study, it has been tried to accomplish alone as a single particular active drug. During tablet formulation, there were many challenges faced by conventional methods, such as the problems made by the formulation, the milling process sometimes causes fines resulting in spots, hardness, etc., some failure compressions and some ejection issues that may result in too dry or too wet tablets often. All these problems can be avoided through using 3D printers as the 3D printer provides a unique formulation so that it can be manufactured not so wet and not so dry tablet specifically. Also with a 3D printer, human errors can be avoided. The ingestion of tablets that can be delivered orally is the most utilized method of drug administration. Tablets are typically processed using single or multiple compressions [25–27].

Conventionally, the tablets were compressed by grinding, mixing and granulation processes to produce the powdered tablets, producing tablets that could be dry or wet according to the manufacturing process. [28,29]. In large-scale industries with huge production lines to be processed under strict controls, the tablets are manufactured around the world to ensure the safety and depth examination of the drug in the tablets. [30]. The studies based on previous research findings demonstrate the benefits of the printed drug product. Drugs like paracetamol, ophylline and caffeine could also be produced in the inkjet printer [31]. The drug has, moreover, has been seen to accumulate just a few micrograms. To manufacture the solid dosage types, a versatile, multi-step 3D printing system was introduced [22,32]. In order to overcome all these high-cost tablet formulations and manufacturing processes, compared to these big pharmaceutical firms, the use of 3D printed tablets costs very little to manufacture. It aims to achieve this objective by using the 3D printer (a 3D printer mounted on a desktop) and its applications. The use of 3D printers has allowed the development of viable 3D printed tablets that can be immediately and sustainably released.

3. METHODOLOGY

3.1 Design of the Experiment

Following is the design of the experiment:

3.1.1 Preparation steps for aloe-vera powder paste

3.1.1.1 Proposed for immediate release layer

Microcrystalline cellulose (MCC) and sodium carboxymethyl cellulose (SSC) needed excipients, which were mixed minimum for 30 minutes of time interval, along with the Aloe-Vera powder intended for immediate release layer. Hypromelose 2910 (1% weight/volume), which was used in the powder blend as a binder. Hypromelose 2910 gel (previously modified volume) was then blended until the paste becomes homogeneous and no separation and aggregates are observed.

3.1.1.2 Proposed for sustained release layer

Hypromelose 2208 (with different percentages) and Poly Acrylic Acid (PAA) were mixed for a minimum for 30 minutes with the Aloe-Vera powder along with the necessary excipients intended for the sustained release layer being used. Whereas Hypromelose 2208 (1 percent w / v) was utilized as the bind of the Aloe-Vera powder used to carry all other paste-forming ingredients collectively.

By utilizing software (FabStudio) in the 3D printer, every arranged pastes was individually packed into distinct syringe tools & put on the 3D printer, and then Aloe-Vera bi-layered tablets were extruded from the 1.2 mm nozzles.

3.1.2 Hypromelose gel preparation

Hypromelose has various viscosity levels that are used for the instant released layers and for the constant released layers.

Hypromelose 2910 (*1% w/v) preparation proposed in gel form:* A one-gram quantity of Hypromelose 2910 powder was taken and introduced to the hot water (around 30 ml near the boiling water level) and mixed thoroughly for around 25-30 minutes. Stirring would then be done in such a way that it gets blended adequately and attained proper dispersion. It is then applied to ice cubes of about seventy grams and then firmly stirred, improving the waters polymer solubility of the Hypromelose content. This gel (gel-like mixture) is then placed in the refrigerator where it can be preserved for at least 24 hours in order to release air bubbles and generate a high concentration of homogeneous gel. [33].

Hypromelose 2208 (*1% w/v) preparation proposed in gel form:* A one-gram quantity of Hypromelose 2208 powder was taken and introduced to the hot water (around 30 ml near the boiling water level) and mixed thoroughly for around 25-30 minutes. Stirring would then be done in such a way that it gets blended adequately and attained proper dispersion. It is then applied to ice cubes of about seventy grams and then firmly stirred, improving the waters polymer solubility of the Hypromelose content. This gel (gel-like mixture) is then placed in the refrigerator where it can be preserved for at least 24 hours in order to release air bubbles and generate a high concentration of homogeneous gel. [33].

3.2 Sample Materials

- Aloe-Vera powder (from Bixa botanical).
- Hypromelose

  a. Hypromelose 2910 (from Sigma-Aldrich)
  b. Hypromelose 2208 (from Colorcon)

- Microcrystalline cellulose (from Sigma-Aldrich)
- Sodium Carboxymethyl Cellulose (SCC) (from Sigma-Aldrich)
- Poly (acrylic acids) (PAA) (from Sigma-Aldrich)
- Trisodium Phosphate Dodecahydrate (from Sigma-Aldrich)

3.3 Instrument

- The 3D printer (on the desk-top) with x-y axis tray movement was used to get the 3D tablets printed. The movement of two nozzles in the z-axis was used to extrude bi-layered tablets of Aloe-Vera bi-layered tablets.
- For in-vitro release (Dissolution Tester-by Erweka, Dt600), the United States Pharma-copeial (USP) Convention Type-I apparatus was used to produce a low pH or acidic medium, representing the human stomach.
- C50 Hardness tester, by I Holland Ltd.
- Friability tester E-1851, Erweka.

3.4 Data Collection

Table 1. Composition of different constituents for immediate release

Compositions constituent	(Percentage w/w) per Immediate Release layer
Aloe-Vera	77
MCC (disintegrant)	13
SCC (disintegrant)	6.5
Hypromelose 2910 (binder)	3.5

Table 2. Composition of different constituents for sustained release

Compositions constituent	Hypromelose 2208 combined with the active drug ingredient			
	6% w/w	8% w/w	10% w/w	14% w/w
Aloe-Vera	87	85	83	79
Hypromelose 2208 (hydrophilic matrix)	6	8	10	14
Poly Acrylic Acid (hydrophilic matrix)	3.5	3.5	3.5	3.5
Hypromelose 2208 (binder)	3.5	3.5	3.5	3.5

3.5 Data Analysis

Sodium carboxymethyl cellulose (SSC) and microcrystalline cellulose (MCC) are the types of disintegrants used to examine the immediate release functionality cited in Table 1 & 2. F Utilizing hydrophilic matrix; poly acrylic acid (PAA) and Hypromelose 2208, at four different percentages of Hypromelose 2208 [(6 percent w / w), (8 percent w / w), (10 percent w / w), (14 percent w / w)] potential of sustained release was checked.

A desktop-based 3D printer was used in the extrusion of bi-layered Aloe-Vera tablets (utilizing FabStudio software) for higher accuracy. Using only a 3D printer that formulates several sustained release tablets, Aloe-Vera bi-layered tablets containing Aloe-Vera powdered paste (as an active drug) are printed.

3.5.1 Investigating *In-vitro* drugs discharge

For the in-vitro discharge, a type I US Pharma-copeial apparatus was utilized with 3D printed tablets in an acidic medium which represented the stomach area of human body, for two hours at 50 rpm. A solution of trisodium phosphate dodecahydrate with a concentration of 0.2 M is then added, increasing the level of pH to approximately 6.8 and representing the gastrointestinal fluid.

In the acidic medium 0.1 M HCl, five 3D printed tablets randomly taken and added in quantity of 675 ml. Then approximately 5 ml of acidic solution samples were taken out for 15, 30, 60, and 120 minutes. After two hours of time was being reached, 0.2 M concentration of tri-sodium phosphate dodecahydrate solution was easily supplemented to it and increased the pH of the solution to 6.8 [34].

By the addition of few drops of HCl solution with 0.2 M concentration in it, the pH can be reversed. Subsequently, 5 ml sample volume at periods of two, four, six, eight, and ten and twelve hours was carried out. And afterwards the visible UV-spectrophotometer then used analyze 1 ml of solution obtained after diluting this with the appropriate dissolution medium from each 5 ml sample solution (taken 9 ml in quantity and at a temperature of 98.6 °C ± 0.5ºC).

3.5.2 Material classification of 3D printed tablets

3.5.2.1 Weight

The percentage of weight differences for twenty tablets was determined and further linked to their average weight [35,36].

3.5.2.2 Friability

18-20 3D printed tablet numbers are selected at random and dusted using a soft brush dusted for loose dust, if any. Every tablets weight is subsequently collected and put on the friability tester where it is rotated for some amount of time (5 minutes) at a constant rotational speed (25rpm). Now these tablets have been dusted with a brush again and then weighted again and the percentage of loss is assessed [35–37].

3.5.2.3 Hardness

The 3D tablets built should be fragile, and the material should be easy to disintegrate and release, although it should be robust enough to prevent rapid breakage during transport and storage. Five 3-dimensional printed tablets are collected and tested for hardness on a test unit. (C50, hardness tester, by I Holland) [35,36,38].

4. RESULTS AND DISCUSSION

Release of active drug initially burst (within 0.5 hours, lesser than 20%) by the designed tablet for immediate discharge. The discharge of the instant discharge layers were optimum because the high volume of the active drug is released due to the disintegrants introduced in the tablet formulation. The initial release of the active drug

with Hypromelose 2208 at 6 percent w / w and 8 percent w / w was found to be good (> 70 percent) over the initial release of the active drug with Hypromelose 2208 as compared with 10 percent w / w and 14 percent w / w (approximately 55 percent or above). Due to some small channels found on the surfaces side of the 3-Dimensional prints tablets, this occurred. The released active drug was found to be consistent with 14% w / w Hypromelose 2208 and decreased when the amount of Hypromelose 2208 increased compared to the release of the active drug. The rise in Hypromelose leads to higher water absorption, improved wetting ability and greater swelling of the formulation of the gel barrier and the hydrophilic matrix that is consistent with the decrease in the rate of drug release with higher levels of Hypromelose 2208 [37]. Apparently, the results shown for both the sustained release and immediate release with the Aloe-Vera as an active drug, it is found that the Aloe-Vera, as an active drug in the immediate release shows much better release as compared to the sustained releases. The 3D printed tablets dissolution can be seen in Fig. 3.

The graph (Fig. 3) indicates the release of Aloe-Hypermellose drug percentage with different w/w concentrations of Hypermellose 2208 with respect to time. As per the mentioned Fig. 3, out of the dissolution profiles of Hypromelose 2208 with different concentrations along with Aloe-Vera, 14% w/w shown to be most consistent dissolution out of the others.

4.1 Tested Mechanical Properties of 3-Dimensional Print Tablets

The mechanical characteristics of 3-Dimensional print tablets were evaluated as per USP specifications for the requisites-hardness, friability, and weight variation [38]. The overall mass can vary slightly during formulation and the weights of all the printed tablets can range from 650 mg to around 750 mg, which is a range for many two-layer industrial tablets. In contrast to other concentrations, Hypromelose 2208 6% w / w 3D printed tablet with the active drug was reported to have the highest differences. This will be checked by altering the formulation. This can be observed that the physical structure of the 3D printed tablets without loss has been treated and processed. In the immediate layer, the factor friability has variability owing to lower % of binder as well as lower viscus grades of the Hypromelose 2910, 1 percent w/w which is also a binding agent [39]. Hypromelose 2800s friability including the active drug 14 percent w / w was found up to point.

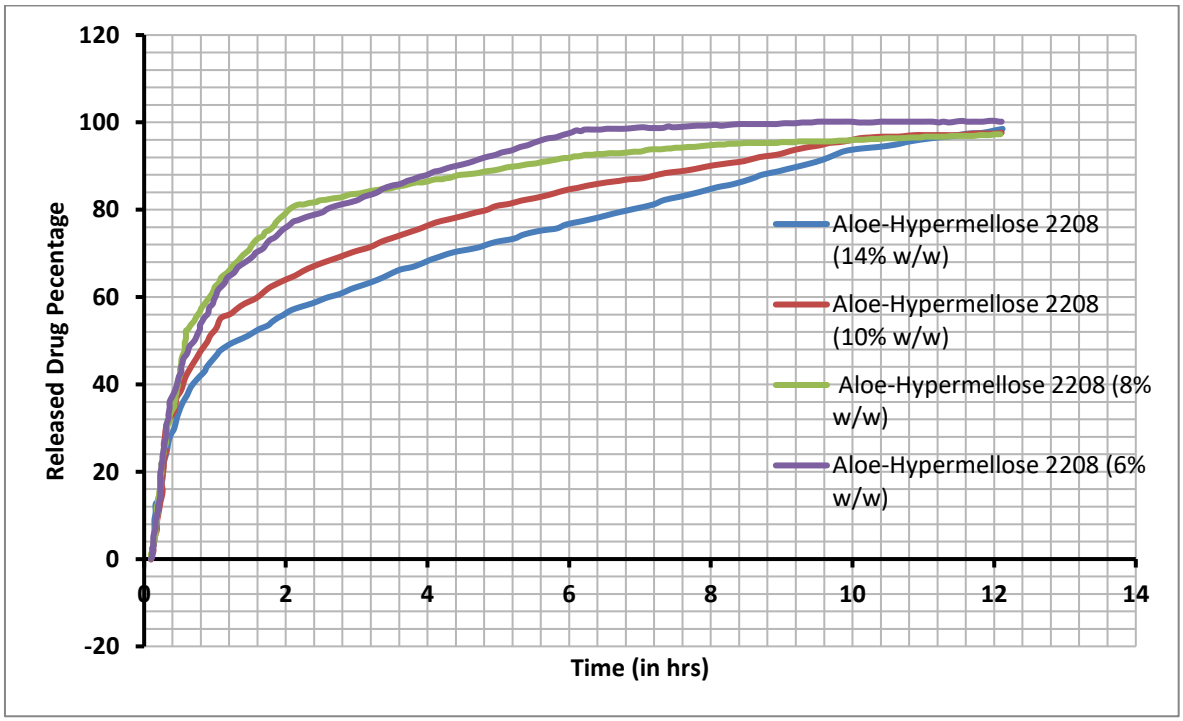

Fig. 3. Dissolution profiles of Hypromelose 2208 [(6%, 8%, 10%, and 14% w/w)] with Aloe-Vera is shown in the graph

4.2 Printed Drug Release Mechanism of the Drug

With acidic conditions, the drug is released within the first two hours of the cycle and released within 2 hours to 12 hours under buffer conditions [37,40,41].

In the current analysis, the developed method of producing bi-layered 3D printed Aloe-Vera tablets provides durability such that tablets are less subjected to be shattered into fragments during storage and transport and are potent enough to dissolve easily when ingested. The kinetics of drug release can be shown, suggesting that immediate release can be achieved between 2-14 hours from a time period of 0-2 hours and continuous release of the drug. Integrated 3D printing software also makes the tablet cost-effective.

5. CONCLUSION

Using a 3D printer, Aloe-Vera bi-layer tablets and their complex composition were being extruded through a cost-effective technique. In the field of pharmaceutical sciences, 3D printing technologies are rapidly evolving, allowing the complicated process to be carried out in a very cost-effective and time-efficient manner that will increase production volumes and make the cost of tablets economical. For the production of modern bi-layer or multi-layer drugs and new tablet designs, 3D printers can be used. The 3D printing of extruded tablets can in some way work together to make a healthier world. Utilizing different analyses and techniques, the bi-layered tablets produced were developed so that the properties set here by tablets were not affected. Individually, the immediate release and the sustained release processes were investigated. The final phase of the study is accomplished without altering the established mechanical properties of the tablet when the 3D printed tablets with specified time periods for immediate and sustained release are obtained. The technique includes an entirely pure tablet to aid some vegan consumers, and as such it does not have any negative impacts, but it can be used as a replacement.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Aloe Vera Farming | Aloe Vera Information. Available:https://www.apnikheti.com/en/pn/agriculture/horticulture/medicinal-plants/aloe-vera.
2. Ni Y, Turner D, Yates KM, Tizard I. Isolation and characterization of structural components of Aloe vera L. leaf pulp; 2004.
DOI: 10.1016/j.intimp.2004.07.006
3. Aloe vera Leaves Powder Aloe barbadensis – Bixa Botanical.
Available:https://bixabotanical.com/products/aloe-barbadensis
4. Lucini L, Pellizzoni M, Pellegrino R, Pietro Molinari G, Colla G. Phytochemical constituents and in vitro radical scavenging activity of different Aloe species, Food Chem; 2015.
DOI: 10.1016/j.foodchem.2014.08.034
5. Chang XL, Chen BY, Feng YM. Water-soluble polysaccharides isolated from skin juice, gel juice and flower of Aloe vera Miller, J. Taiwan Inst. Chem. Eng; 2011.
DOI: 10.1016/j.jtice.2010.07.007
6. Boudreau MD, Beland FA. An evaluation of the biological and toxicological properties of Aloe barbadensis (Miller), Aloe vera, Journal of Environmental Science and Health - Part C Environmental Carcinogenesis and Ecotoxicology Reviews; 2006.

DOI: 10.1080/10590500600614303.
7. Gioumouxouzis CI, et al. Fabrication of an osmotic 3D printed solid dosage form for controlled release of active pharmaceutical ingredients, Eur. J. Pharm. Sci. 2020; 143:105176.
DOI: 10.1016/j.ejps.2019.105176
8. Melocchi A, et al. Expandable drug delivery system for gastric retention based on shape memory polymers: Development via 4D printing and extrusion, Int. J. Pharm; 2019.
DOI: 10.1016/j.ijpharm.2019.118700
9. Siamidi A, Tsintavi E, Rekkas DM, Vlachou M. 3D-printed modified-release tablets: A review of the recent advances, in molecular pharmacology; 2020.
10. Fina F, Goyanes A, Gaisford S, Basit AW. Selective laser sintering (SLS) 3D printing of medicines, Int. J. Pharm; 2017.
DOI: 10.1016/j.ijpharm.2017.06.082
11. Trenfield SJ, Awad A, Goyanes A, Gaisford S, Basit AW. 3D printing pharmaceuticals: Drug development to frontline care, trends in pharmacological sciences; 2018.
DOI: 10.1016/j.tips.2018.02.006
12. Aho J, Bøtker JP, Genina N, Edinger M, Arnfast L, Rantanen J. Roadmap to 3D-printed oral pharmaceutical dosage forms: Feedstock filament properties and characterization for fused deposition modeling. Journal of Pharmaceutical Sciences; 2019.
DOI: 10.1016/j.xphs.2018.11.012
13. Nasereddin JM, Wellner N, Alhijjaj M, Belton P, Qi S. Development of a simple mechanical screening method for predicting the feedability of a pharmaceutical FDM 3D printing filament, pharm. Res; 2018.
DOI: 10.1007/s11095-018-2432-3
14. Sadia M, et al. Adaptation of pharmaceutical excipients to FDM 3D printing for the fabrication of patient-tailored immediate release tablets, Int. J. Pharm; 2016.
DOI: 10.1016/j.ijpharm.2016.09.050
15. Boetker J, Water JJ, Aho J, Arnfast L, Bohr A, Rantanen J. Modifying release characteristics from 3D printed drug-eluting products, Eur. J. Pharm. Sci; 2016.
DOI: 10.1016/j.ejps.2016.03.013
16. El Aita I, Breitkreutz J, Quodbach J. On-demand manufacturing of immediate release levetiracetam tablets using pressure-assisted microsyringe printing, Eur. J. Pharm. Biopharm; 2019.
DOI: 10.1016/j.ejpb.2018.11.008
17. Castellano JM, et al. A polypill strategy to improve adherence: Results from FOCUS (Fixed-dose Combination Drug for Secondary Cardiovascular Prevention) Project, J. Am. Coll. Cardiol; 2014.
18. Pietrzak K, Isreb A, Alhnan MA. A flexible-dose dispenser for immediate and extended release 3D printed tablets, Eur. J. Pharm. Biopharm; 2015.
DOI: 10.1016/j.ejpb.2015.07.027
19. Sadia M, Arafat B, Ahmed W, Forbes RT, Alhnan MA. Channelled tablets: An innovative approach to accelerating drug release from 3D printed tablets, J. Control. Release; 2018.
DOI: 10.1016/j.jconrel.2017.11.022
20. Jamróz W, Kurek M, Czech A, Szafraniec J, Gawlak K, Jachowicz R. 3D printing of tablets containing amorphous aripiprazole by filaments co-extrusion, Eur. J. Pharm. Biopharm; 2018.
DOI: 10.1016/j.ejpb.2018.07.017
21. Alhnan MA, Okwuosa TC, Sadia M, Wan KW, Ahmed W, Arafat B. Emergence of 3D printed dosage forms: Opportunities and challenges, pharmaceutical research; 2016.
DOI: 10.1007/s11095-016-1933-1
22. Rowe CW, Katstra WE, Palazzolo RD, Giritlioglu B, Teung P, Cima MJ. Multimechanism oral dosage forms fabricated by three dimensional printing(TM), J. Control. Release; 2000.
DOI: 10.1016/S0168-3659(99)00224-2
23. Organic Aloe Vera Powder.
Available:https://www.tradeindia.com/fp6274596/Organic-Aloe-Vera-Powder.html
24. The Formulators Guide to Aloe Vera in Natural Skincare - Formula Botanica.
Available:https://formulabotanica.com/aloe-vera-in-skincare-formulation/
25. Sastry SV, Nyshadham JR, Fix JA. Recent technological advances in oral drug delivery - A review, Pharmaceutical Science and Technology Today; 2000.
DOI: 10.1016/S1461-5347(00)00247-9
26. Jivraj M, Martini LG, Thomson CM. An overview of the different excipients useful for the direct compression of tablets, Pharmaceutical Science and Technology Today; 2000.
DOI: 10.1016/S1461-5347(99)00237-0
27. Rosca ID, Vergnaud JM. Evaluation of the characteristics of oral dosage forms with

release controlled by erosion, Comput. Biol. Med; 2008.
DOI: 10.1016/j.compbiomed.2008.03.001
28. Parmar J, Rane M. Tablet formulation design and manufacture: Oral immediate release application, Pharma Times; 2009.
29. GM. Pharmaceutical preformulation and formulation: A practical guide from candidate drug selection to commercial dosage form. New York; 2009.
30. Scoutaris N, Alexander MR, Gellert PR, Roberts CJ. Inkjet printing as a novel medicine formulation technique, J. Control. Release; 2011.
DOI: 10.1016/j.jconrel.2011.07.033
31. Sandler N, et al. Inkjet printing of drug substances and use of porous substrates-towards individualized dosing, J. Pharm. Sci; 2011.
DOI: 10.1002/jps.22526
32. Katstra WE, Palazzolo RD, Rowe CW, Giritlioglu B, Teung P, Cima MJ. Oral dosage forms fabricated by Three Dimensional Printing(TM), J. Control. Release; 2000.
DOI: 10.1016/S0168-3659(99)00225-4
33. Abd-Allah FI, Dawaba HM, Ahmed AM. Preparation, characterization, and stability studies of piroxicam-loaded microemulsions in topical formulations, Drug Discov. Ther; 2010.
34. Blume RW, Davis RD, Keyser DJ. Guaifenesin sustained release formulation and tablets, US 6,372,252 B1; 2002.
35. Remington JP, Beringer P. Remington : The science and practice of pharmacy. Philadelphia: Lippincott Williams & Wilkins; 2006.
36. Bushra R, Shoaib MH, Aslam N, Hashmat D, Masud-Ur-Rehman. Formulation development and optimization of ibuprofen tablets by direct compression method, Pak. J. Pharm. Sci; 2008.
37. Folttmann H, Quadir A. Copovidone - a copolymer with unique formulation properties., Drug Deliv. Technol; 2008.
38. United States Pharmacopeial Convention, The United States Pharmacopeia : USP 24 : the National Formulary : NF 19, March 9-12, 1995 ; Rockville, Md. Rockville, Md.: United States Pharmacopeial Convention; 1999.
39. Nagadivya P, Ramakrishna R, Sridhar G, Bhanushashank R. Effect of various binding agents on tablet hardness and release rate profiles of diclofenac sodium tablets, Int. J. Res. Pharm. Sci; 2012.
40. Patra CN, Kumar AB, Pandit HK, Singh SP, Devi MV. Design and evaluation of sustained release bilayer tablets of propranolol hydrochloride, Acta Pharm; 2007.
DOI: 10.2478/v10007-007-0038-0
41. Bijank G, Rabindra D, Soumyadeep G, Manas C, Amitava B. Formulation development studies of bilayer tablet glipizide: A novel and evolutionary approach in the treatment of diabetes, Asian J. Pharm. Clin. Res; 2013.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/73346