



Controlled Release of Bi-Layered Delphinidin Tablets Using 3D Printing Techniques

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Authors' contributions

This work was carried out in collaboration between both authors. Author TK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors TK and SKS managed the analyses of the study. Author SKS managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Delphinidin is a known dye and food colorant along with many medicinal properties for instance anti-inflammatory, anti-microbial, anti-diabetic, anti-obesity and anti-cancer. The present research has been designed to formulate bi-layered tablets using delphinidin which inherits these medicinal properties. The extrusion of tablets is done by using 3D printing techniques involving a table-top 3D printer which extrudes delphinidin tablets along with the required excipients. The characteristics of the whole tablets have been analyzed separately including hardness, friability, and weight. Adapted method for tablet formulation results in tablets which are appropriate for the immediate release and sustained release. The present research provides a method to make the effective tablets with reduced cost which can be used as drug formulation method in pharmaceutical industries.

Keywords: Anthocyanidin; bi-layer tablets; delphinidin; 3d printer.

1. INTRODUCTION

Delphinidin is an anthocyanidin which can be obtained from bilberries and other pigmented

fruits and flowers. Anthocyanidin is a natural pigment which is the precursor anthocyanins which gives us the blue-red colours of fruits and flowers [1]. Delphinidin releases the nitric oxide

by the vascular endothelium which causes vasorelaxation [2]. Delphinidin also inhibit signaling obtained by the epithelial growth factor receptors which on the other hand suppressing the estrogen receptor expression and apoptosis and autophagy are induced at 1-40 μM of dose [3,4]. The structural formula of the delphinidin is shown in Fig. 1.

Anthocyanins apart from their colour properties has various health attributes such as anti-inflammatory effects, anti-carcinogen activity, reduced coronary diseases risk and improved cognitive behavior [5,6]. Just like pH paper, anthocyanin appears to be red in colour when present in the acidic condition and blue in colour when present in alkaline medium. Anthocyanins depends on temperature, light, pH, and its structure in the regards to its stability [7].

Fruits, tubers, flowers are prominent sources of blue, red, purple pigments which constitutes anthocyanins. Anthocyanins in plants are very useful as the pigments are extracted from the plant sources like fruits, flowers, vegetables, and are traditionally used as food colorants. Besides these various uses of anthocyanins it is also found to exhibit medical properties such as anti-inflammatory, anti-cancer, anti-microbial, anti-diabetic, anti-obesity and also preventing the cardiovascular diseases [8]. There are various types of anthocyanins can be found in plants some of them are shown below with their structures in Fig. 2.

The soluble nature of pigments of anthocyanin: Anthocyanins are found in several grapes and

wines as flavylium ion. Flavylium ion converts into carbinol pseudo-base, chal-cone or quinoidal-base when its pH gets increased before being getting absorbed into blood stream [9]. As mentioned previously about the pigments of anthocyanin that it appears blue or purple in alkaline medium and red in acidic medium and are extracted from the flowers and fruits, red and purple berries. So it is found that water serves as an extraction medium for anthocyanin. This is because water serves as solving medium for anthocyanin as anthocyanin are soluble in water as well as organic solvents [10]. The structure of flavylium ion can be seen below in Fig. 3.

Plants used in the extraction of delphinidin: Various coloured berries, flowers, flowers are used in the extraction of the delphinidin. In the present research, delphinidin as an extract of maqui berry is obtained by Delphinol which contains total delphinidin $\geq 25\%$ and total anthocyanins $\geq 35\%$ [11].

About Maqui Berry: Maqui Berry or *Aristotelia chilensis* (Family: *Elaeocarpaceae*) is a very powerful form of antioxidant super-fruit, is a native to Chile and only grows in the forests present in the south of Chile. This berry has been consumed from ancient times by the indigenous people. Maqui Berries are considered to be rich in anthocyanins, delphinidin, and polyphenols. Maqui Berry grows like evergreen bush and reaches up to 4m in height Maqui Berry, apart from their colour properties have various health attributes such as anti-inflammatory effects, anti-aging effect, and anti-oxidant [12].

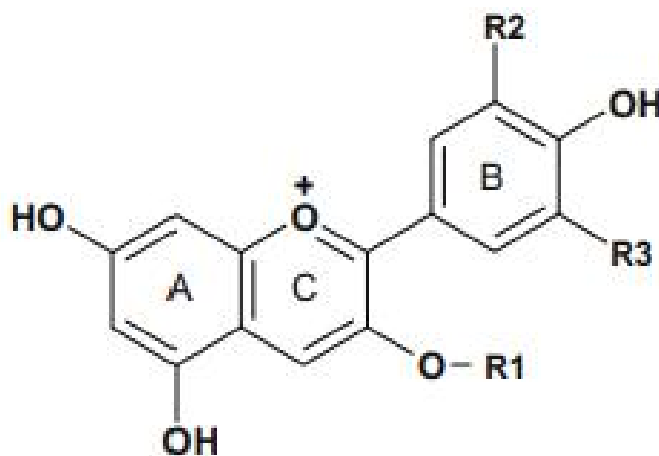


Fig. 1. Structure of delphinidin (Here R1 = H; R2 = OH; R3 = OH) [5]

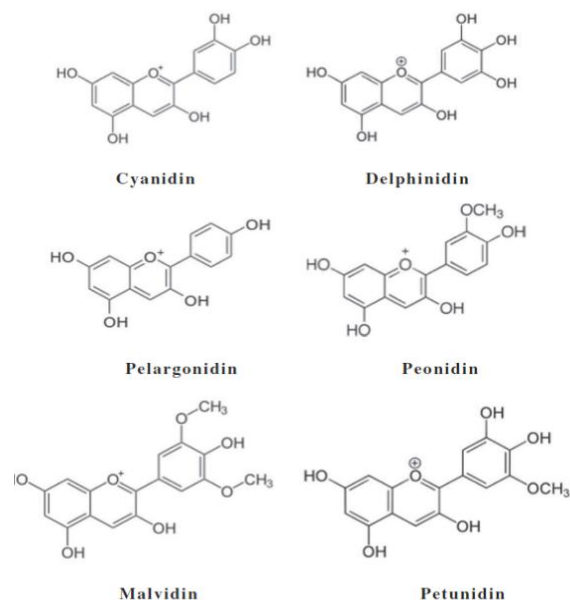


Fig. 2. Major sources of anthocyanidins found in plants [10]

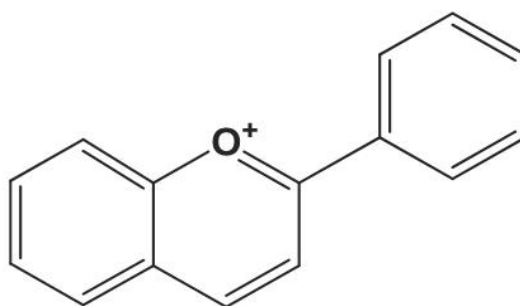


Fig. 3. Structure of flavylium ion in two dimensional views [10]

The objective of the present research leads to the creation of effective tablets without affecting the medicinal properties of delphinidin using a low cost method comprising a 3D printer. In the various areas of engineering, aerospace, construction automobiles, dentistry, robotics, etc., use of such 3D printing technologies is already present in manufacturing new things but in pharmacy its usage cannot be seen as it is seen in other fields [13].

History of tablet printing using 3D printing techniques:

As the first 3D printed drug was approved through us food and Drug Administration in 2015, the technology was used to advance the pharmaceutical industry that eventually boosts healthcare sectors. In the pharmaceutical

industries, the boost of powder of powdered tablets created using 3D printer was raised between the years 1993-2003 that leads to the oral dosage forms [14]. After that the industry keeps on advancing.

There were many problems that were faced during the tablet formulation by conventional methods such as the defects which are caused by the formulation, the milling process also causes fines which results in the spots, hardness, etc., some failure compressions and some ejection problems which might results in sometimes too dry or too wet tablets [15]. But using 3D printer these all problems can be avoided as the 3D printer provides precise formulation and compositions so exactly not so wet and not so dry tablet can be created. 3D printer also minimizes human errors.

In the preparation of tablets, the method involving single or multiple compressions are widely used and the intake of tablets orally is mostly used way of consumption [16-18]. The conventional method of production of the powdered tablets was the compression of tablets through mills, mixing and granulation units that creates tablets which could be dry or wet as per its method of production [19,20]. Tablets are manufactured in large scale in huge plants all over the world in industries with some rules and regulation [21]. But this way it costs very much for the production of tablets. The previous researches show the printing of medicines from the inkjet printers used for depositing the drugs like paracetamol, theophylline, and caffeine [22]. But in this method of using the inkjet printer, few micrograms of the drug could be seen to be deposited. So for printing the complex solid dosage tablets which involves multiple step process a 3D printer was imported [14,23].

These methods costs very high so the present research incorporates a method which is formulate bi-layered tablets precisely as the use of a 3D printer based on a desktop allow achieving this. The tablets which are manufactured here by using 3D printing techniques are capable of immediate and sustained releases.

2. RESEARCH QUESTIONS

Can there be a cost effective methods to manufacture bi-layered tablets and attain controlled drug release?

3. METHODOLOGY

3.1 Design of Experiment

The present research experiment follows steps that are:

Hydroxy Propyl Methyl Cellulose or HPMC used for immediate release [HPMC 2910 (1 percent w/v)] and for the sustained release [HPMC 2208 (1percentw/v)] and are having different level of viscosity grades of HPMC.

3.1.1 Gel form preparation of HPMC 2910 (1% w/v)

The powder of HPMC 2910 taken in 1 gram of quantity and then approx. 30 ml water, near to boiling water level is added to it and agitated around 20-30 minutes. After agitating, it is

thoroughly mixed to form a good dispersion. After that 70 grams of ice-cubes are added to it and it is again agitated strictly so that it increases the polymer solubility of HPMC powder in the water. Afterwards the gel-suspension is kept into the refrigerator and stored for around minimum of 24 hours which makes it free from air bubbles, and a consistent and smooth homogenous gel is formed [24].

3.1.2 Gel form preparation of HPMC 2208 (1% w/v)

The powder of HPMC 2208 taken in 1 gram of quantity and approx. 30 ml water, near to boiling water level is added to it and agitated for around 20-30 minutes. After agitating it is thoroughly mixed to form a good dispersion. After that 70 grams of ice-cubes are added to it and then it is again agitated strictly so that it increases the polymer solubility of HPMC powder in the water. Afterwards the gel-suspension is kept into the refrigerator for around minimum 24 hours which makes it free from air bubbles, and a consistent and smooth homogenous gel is formed [24].

3.2 Delphinidin Paste Preparation

3.2.1 Intended for immediate release layer

The required excipients with the delphinidin powder for immediate release layer used here are sodium starch glycolate (SSG) and microcrystalline cellulose (MCC) and are mixed thoroughly for around minimum of 30 minutes of time. HPMC 2910 (1% w/v) has been used as binder in the powder blend. Now pre-adjusted amount of HPMC 2910 gel is blended till the paste appears homogenous so that no observation of aggregates and separation should be found.

3.2.2 Intended for sustained release layer

The required excipients with delphinidin powder for sustained release layer used here are the different percentages of HPMC 2208 and Poly Acrylic Acid (PAA) which are mixed thoroughly for about minimum of 30 minutes. On the other hand, HPMC 2208 (in 1% w/v) is also as binder is utilized for the delphinidin powder because it to holds all the ingredients collected for the formation of paste.

Afterwards different syringe tool of the 3D printer with 1.2 mm nozzles are used where each prepared paste is filled separately to extrude bi-

layered tablets of delphinidin using a 3D printer based on software (Fab Studio).

- Trisodium Phosphate Dodecahydrate (Sigma-Aldrich)

3.3 Sample Materials Taken

- Delphinidin powder (Appearance: Purple powder) acts as the active component. (From Delphinol, MNL, maqui berry standard extract and contains delphinidin \geq 25%)
- Hydroxy propyl Methyl cellulose (HPMC)
- HPMC 2910 (Hypromellose, Sigma-Aldrich)
- HPMC 2208 (Methocel K100M Premium, Colorcon)
- Microcrystalline cellulose(MCC is by Pharmacel of 102)
- Sodium Starch Glycolate(SSG by Primojel)
- Poly Acrylic Acid(PAA from carbopol 974P NF, by Surfachem Group)

3.4 Instruments Used

- 3D Printer (Desk-top) with a tray that shows movement in x-y axis which is used to get the 3D printed tablets and the nozzles shows movement in the z-axis which is used to extrude the delphinidin bi-layer tablets.
- United States Pharmacopeial (USP) Convention Type-I apparatus is used for in-vitro release (Dissolution Tester-Erweka of variant Dt600) which creates a low pH or acidic medium that represents the human stomach.
- C50 Hardness tester, by I Holland Ltd.
- Friability tester E-1851, Erweka.

3.5 Data Collection

Table 1. Composition of constituents for immediate release

Constituents of composition	(Percentage w/w) per IR layer
Delphinidin	76
MCC PH 102 (disintegrant)	12
SSG type A (disintegrant)	9.2
HPMC 2910 (binder)	2.8

Table 2. Composition of constituents for sustained release

Constituents of Composition	HPMC2208 combined with the active drug ingredient			
	6% w/w	8% w/w	10% w/w	14% w/w
Delphinidin	89	87	85	81
HPMC 2208 (as hydrophilic matrix)	6	8	10	14
Poly Acrylic Acid (hydrophilic matrix)	2.5	2.5	2.5	2.5
HPMC 2208 (binder)	2.5	2.5	2.5	2.5

3.6 Data Analysis

Various disintegrants have been used to test the usefulness of immediate release. Referring to Tables 1 & 2 the disintegrants that have been used are the microcrystalline cellulose (or MCC) and the sodium starch glycolate (SSG). The sustained release functionality is examined with the aid of hydrophilic matrix; poly acrylic acid (PAA) and HPMC 2208 used as the four different percentage value of HPMC2208 [(6% w/w), (8% w/w), (10% w/w), (14% w/w)].

A desktop based 3D printer used for the extrusion of delphinidin bi-layered tablets (using the software FabStudio which is used for both immediate and sustained release drug formulation.

3.6.1 In-vitro drug release analysis

The U. S. Pharmacopeial (USP) Convention of Type-I apparatus is used in the in-vitro release of the drug with 3D printed tablets at around 50rpm within the acidic medium (which is representative of the stomach) for 120 minutes. Trisodium phosphate dodecahydrate solution with 0.2 M concentration is

added afterwards which is used to increase the pH level to about 6.8 and it will then represent the gastrointestinal fluid. Randomly five numbers of 3D printed tablets are added to the acidic medium of 675ml of quantity of concentration 0.1M HCl. Then 5 ml samples are taken out from the acidic solution at 0.25, 0.5, one, and two hours of intervals [25]. Trisodium phosphate dodecahydrate solution of 0.2M solution are added to it quickly after when the two hours of time interval has been completed which increases the pH of the solution to 6.8 [25]. For instance, if pH value has increased more than the desired value at that time it can be adjusted by addition of few drops of HCl solution of concentration 0.2 M, subsequently, a sample of 5ml quantity at 02, 04, 06, 08, and 10 and 12 hours of time intervals have taken out. Afterwards a UV-Visible spectrophotometer used to analyze the 1ml solution which is taken from each of the 5ml sample solution after diluting it with a suitable dissolution medium (taken 9ml in quantity and at a temperature of $98.6^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ of temperature).

3.6.2 3D printed tablets and its physical characterization

Weight: 20 individual tablets with their percent of variations in weight were calculated and compared with their average [26,27].

Friability: 15-20 numbers of 3D printed tablets taken at random and are being kept on a sieve to dust the loose dust if it is found any using a soft brush. Then after taking weight of each tablet are then placed on the friability tester where they were rotated with the constant rotation speed (25rpm) for some phase of time (5 minutes). Again the tablets were placed on a sieve and dusted using a brush and then weighted again to calculate the loss percentage [26-28].

Hardness: Printed tablets should be soft and disintegrate quickly and release the medication and, on the other hand, should be strong enough so that it cannot be quickly disintegrated during transport and storage. Here, five 3D printed tablets taken and tested on hardness tester machine. (C50, hardness tester, by I Holland) [26-29].

4. RESULTS AND DISCUSSION

4.1 Dissolution of 3D Printed Tablets

The immediate release layer of the tablet designed has been occurred at the initial burst release of the active drug (less than 20% in 0.5 hours). Due to the disintegrants that are added in formulation of tablets, makes the release of the immediate release good as the high amount of the active drug is released. In two hours of time interval, the immediate release of the active drug with HPMC2208 in 6% w/w and of 8% w/w was noticed high (>70%) as compared to it from the 10% w/w and the 14% w/w (around 55% or more).

This occurred because of some small channels that are found on the surface side of the 3D

printed tablets. Active drug released with 14% w/w HPMC2208 was found to be most appropriate and when the amount of HPMC2208 increases than the active drug's release decreases. Increase in HPMC leads to increase in water uptake, better wettability and greater swelling of the gel barrier formulation and the hydrophilic matrix that are stable to the reduction which is detected in the drug release rate with greater amount of HPMC2208 [28]. The dissolution of drug can be seen in the Fig. 4.

4.2 3D Printed Tablets and Its Mechanical Properties

Complied with USP specifications, the mechanical properties of 3D printed tablets were investigated for factors like hardness, friability, and weight variations [29]. Throughout the formulation, the absolute weight may slightly vary and such that all the printed tablets weights in between 650mg - 750mg which is the already defined range for various commercial bi-layer tablets. Active drug with HPMC2208 6% w/w 3D printed tablet have found to be of having the highest difference compared with among other concentrations. This can be controlled by changing the formulation. The tablets printed with 3D printer could be found to handle and stored with no loss in its structural integrity. Friability factor has variation due to reduced percent of binder, and low viscosity level of the HPMC2900 (1% w/w) in immediate release layer which is also a binding agent [30] and the friability of the active drug with HPMC2800 14% w/w was found to be up to mark.

4.3 Drug Release Mechanism of the Printed Drug

In acidic conditions, the drug released in first two hours of the time period and in the buffer conditions it releases in 2 hours to 12 hours and both the settings are shown in the experiment [28,31,32].

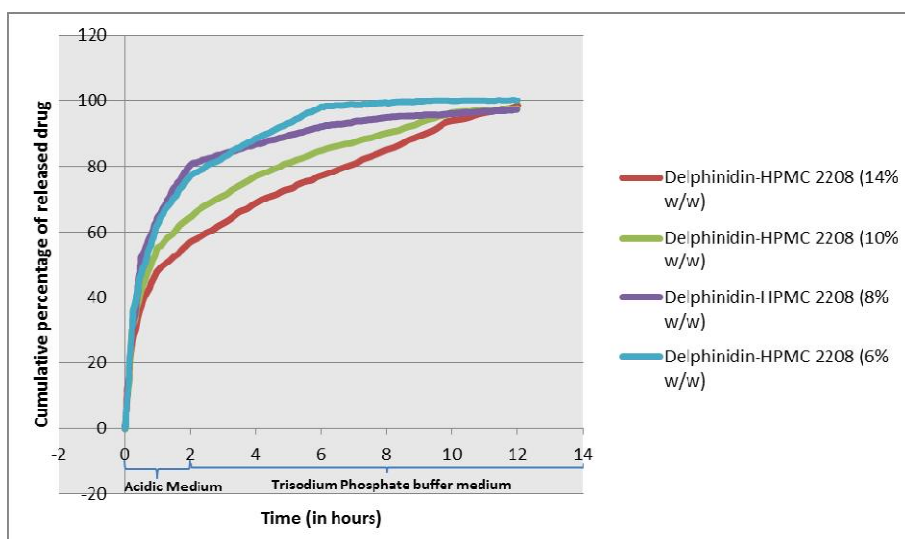


Fig. 4. Delphinidin with HPMC2208 [(6% w/w), (8% w/w), (10% w/w), (14% w/w)] and their dissolution profiles is shown in the graph

Adapted method to create bi-layered 3D printed tablets of delphinine in the present research creates tablets that are strong enough during their storage and transportation to not be split into pieces and are fragile enough to disintegrate easily when eaten. The kinetics of drug release can be seen that shows the immediate release is attained between 0-2 hours of the time intervals and the sustained release of the drug can be obtained within 2-14 hours. Adapted 3D printing technique makes the tablet cost-efficient as well. The technique can be used in tablet manufacturing creating a cost-effective work flow in pharmaceutical industries, however further studies including functional analysis of tablets created by 3D printing can be done in future.

5. CONCLUSION

The complex formulation of bi-layer delphinidin tablets has been extruded using a 3D printer which is a cost-effective way to do the same. 3D printing techniques are developing quickly and, in the pharmaceutical science areas, the complex process can be carried out in a very cost-effective and time-efficient manner, which will increase output levels and also the cost of tablets will be reasonable. The objective of the experiment is to obtain an alternative and low-cost method from that already existing in the industries. The 3D printer can be used to produce new drugs with bi-layer or multi-layer formulations and a new design of printed tablets. In some way, 3D printing extruded tablets will lead to a healthier country. The produced bi-

layered tablets have been designed using a variety of analyzes and methods so that the set properties of the tablets have not been affected. Separately, the immediate release and sustained release approaches were researched. The final stage of the research is completed when the 3D printed tablets with fixed time intervals for immediate and sustained release without modifying the mechanical properties of the tablets are attained.

DISCLAIMER

The products used for this research are commonly and predominantly used 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

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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