UNIVERSITI PUTRA MALAYSIA

DISSOLUTION CHARACTERISTICS OF SELECTED FRUIT TABLETS WITH EFFERVESCENT AGENTS

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DISSOLUTION CHARACTERISTICS OF SELECTED FRUIT TABLETS WITH EFFERVESCENT AGENTS

By

MD. SAIFULLAH

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the degree of Master of Science

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DEDICATION

Abstract of thesis presented to Senate of Universiti Putra Malaysia in fulfilment of the requirements for the degree of Master of Science

DISSOLUTION CHARACTERISTICS OF SELECTED FRUIT TABLETS WITH EFFERVESCENT AGENTS

By

MD. SAIFULLAH

March 2015

Chairman: Associate Professor Yus Aniza Yusof, PhD
Faculty: Engineering

Tableting of fruit powder is a unique technique in the area of fruit powder preservation. Dissolution characteristic of tablet is an important parameter for quality control and production. The acceptability and popularity of fruit powder tablet depend on its dissolution rate. Physicochemical properties of tablet ingredients have great influence on dissolution behaviour of tablet. This research was conducted in two major areas namely determination of physicochemical properties of fruit powder and their relationship with the dissolution of tablet with effervescent agents, and dissolution profiling of fruit powder effervescent tablets and dissolution profile comparison. Pitaya, pineapple, mango and guava fruits were used in this research, as these fruits are grown in large quantity in Malaysia. Tablets with 20 mm diameter and 2.5 gm weight were made by using a direct compression method at a constant pressure via a universal testing machine. Dissolution test was carried out in a dissolution tester and dissolved amount of solute was measured by an Ultraviolet spectrophotometric test as a function of time. Distilled water and simulated saliva was used as dissolution medium in the dissolution test at room temperature and 37^{o}C temperature respectively. The investigation on physicochemical analysis showed that fruit powders were different from each other in terms of physical and chemical properties. The results showed that the fat content in powder has inverse relationship with dissolution rate. On the other hand, porosity of the tablet represented proportional relationship with dissolution rate and application of effervescent agents increased the dissolution rate of tablet significantly. In this study three types of method were adopted to compare the dissolution profile which includes model dependent, model independent and statistical method. Five release kinetics mathematical equations were used to compare dissolution profile in model dependent method. According to model dependent method, when distil water was used as dissolution medium, pineapple, guava and mango powder tablet dissolution profile shows similarity as their dissolution profile was fitted with Higuchi model. However, pitaya powder tablet dissolution profile was different from other types as its dissolution profile was fitted very well with zero order kinetics model. In simulated saliva, same phenomenon was appeared; pineapple, guava and mango powder tablet dissolution profile shows similarity and pitaya powder tablet dissolution profile was different from them. On the other hand, according to model independent method, dissolution profiles of fruit powder tablets were in the similarity range at most

of the points. However, in the statistical method pair-*t* test showed that there was significantly difference among the dissolution profile of fruit powder tablets at the level of $P<0.01$. Based on this study, a better understanding about physicochemical properties of fruit powder and their relationship with dissolution rate and effect of effervescent agents on dissolution rate are obtained, which are essential for processing and handling of fruit powder and tablet preparation as well as improvement of dissolution rate. In conclusion, dissolution profiling and its comparison will be helpful for further change in formulation, development of new formulation, scale up of the production, and quality control in production line during industrial scale production.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperlun untuk Ijazah Master Sains

CIRI-CIRI PELARUTAN TABLET BUAH-BUAHAN TERPILIH DENGAN EJEN PEMBUIHAN

Oleh

MD. SAIFULLAH

Mac 2015

Pengerusi: Profesor Madya Yus Aniza Yusof, PhD
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Pemadatan serbuk buah-buahan dalam bentuk tablet adalah satu teknik yang unik dalam bidang pemeliharaan serbuk buah-buahan. Ciri pelarutan tablet adalah parameter yang penting untuk kawalan kualiti dan pengeluaran. Penerimaan dan popularitи serbuk buah tablet bergantung kepada kadar keterlarutannya. Ciri fiziko-kimia bahan tablet mempunyai pengaruh besar ke atas sifat terlarut bagi tablet. Kajian ini dijalankan dalam dua bidang utama iaitu penentuan sifat fiziko-kimia bagi serbuk buah-buahan dan hubungan mereka dengan sifat terlarut tablet dengan ejen pembuih. Selain itu, corak pelrutan bagi tablet buah yang ditambah agen pembuih dan perbandingan corak pelarutan bagi kesemua tablet buah tersebut. Buah-buahan seperti buah naga, nanas, mangga dan jambu batu telah digunakan dalam kajian ini kerana buah-buahan ini ditanam kuantiti yang banyak di Malaysia. Tablet yang mempunyai ukuran 20 mm bagi diameter dan 2.5 gm bagi berat telah dihasilkan dengan menggunakan kaedah mampatan langsung pada tekanan tetap melalui mesin ujian universal. Tambahan lagi, ujian pelarutan telah dijalankan di dalam alat penguji keterlarutan. Jumlah bahan larut juga telah diukur oleh ujian spektrofotometri ultra-ungu yang berkadar dengan masa. Air suling dan simulasi air liur telah digunakan sebagai medium pelarutan dalam ujian pelarutan pada dua suhu yang berbeza iaitu suhu bilik dan suhu 37^{o}C. Penyelidikan terhadap analisis fizikokimia menunjukkan bahawa serbuk buah adalah berbeza antara satu sama lain dari segi ciri-ciri fizikal dan kimia. Hasil kajian menunjukkan bahawa kandungan lemak dalam serbuk mempunyai hubungan songsang dengan kadar pelarutan. Di samping itu, sifat berongga tablet mempunyai hubungan berkadar terus dengan kadar keterlarutan. Aplikasi ejen pembuih juga meningkatkan kadar keterlarutan bagi tablet buah dengan ketara. Dalam kajian ini tiga jenis kaedah telah digunakan untuk membandingkan profil corak pelarutan tablet buah. Tiga kaedah tersebut ialah model bergantung, model bebas dan kaedah statistik. Lima persamaan matematik bagi kinetik pelepasan telah digunakan untuk membandingkan corak profil pelarutan dalam model kaedah bergantung. Menurut model kaedah bergantung, apabila air suling telah digunakan sebagai medium pelarutan, corak profil pelarutan bagi tablet nanas, jambu batu dan serbuk mangga menunjukkan persamaan kerana corak profil pelarutan bagi ketiga-tiga tablet buah tersebut adalah paling sesuai mengikut model Higuchi. Walau bagaimanapun, corak profil pelarutan bagi serbuk buah naga adalah berbeza daripada serbuk buah yang lain kerana corak profil pelarutan bagi buah naga adalah paling sesuai mengikut model kinetik tertib sifar. Dalam simulasi air liur,

fenomena yang sama telah muncul; nanas, jambu batu dan corak profil pelarutan bagi tablet serbuk mangga menunjukkan persamaan dan corak profil pelarutan bagi tablet serbuk pitaya adalah berbeza dari serbuk buah yang lain. Sebaliknya, menurut kaedah model bebas, corak profil pelarutan bagi tablet serbuk buah berada dalam lingkungan persamaan di kebanyakan titik. Walau bagaimanapun, dalam kaedah statistik pasangan-ujian t menunjukkan tidak terdapat perbezaan ketara antara corak profil pelarutan tablet serbuk buah-buahan di peringkat $P < 0.01$. Berdasarkan kajian ini, pemahaman yang lebih baik tentang sifat fizikokimia serbuk buah-buahan dan hubungan mereka dengan kadar pelarutan serta kesan ejen pembuih pada kadar keterlarutan telah dicapai. Hal yang sedemikian, adalah penting untuk pemprosesan dan pengendalian serbuk buah-buahan dan penyediaan tablet serta peningkatan kadar keterlarutan bagi tablet serbuk buah-buahan. Kesimpulannya, corak profil pelarutan dan perbandingannya akan membantu untuk perubahan lagi dalam penggubalan, pembangunan formulasi baru, peningkatan skala pengeluaran dan kawalan kualiti dalam pengeluaran produk dalam skala industri.

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I certify that a Thesis Examination Committee has met on 2 March 2015 to conduct the final examination of Md. Saifullah on his thesis entitled "Dissolution Characteristics of Selected Fruit Tablets with Effervescent Agents" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of supervisory committee were as follows:

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This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
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CHAPTER 1

INTRODUCTION

1.1 Background of study

Like any other agricultural produce, many different fruits are available in the market at peak season. Due to market saturation, the producers do not get their desired price and sometimes postharvest losses occur. People would typically prefer to consume fresh fruits all the year round, but practically it is impossible to provide fresh fruits all the year round. So, people are usually deprived of the natural taste of fruit in the off season, and producers may face financial losses at peak season. Not all fruits are grown in all areas of the world, and most fruits are produced in the tropical and sub-tropical zones. Hence, people of the temperate zones are deprived of most of the fruits grown in the world. Fresh fruits may be exported to temperate zones, but this will be costly and the risk of spoilage is high.

To reduce these problems, fruits are processed mainly into juice and other products. Among the different types of products, fruit juice is equally popular for people of all age groups in every part of world. However, the production of fruit juice requires a large number of unit operations and thermal processing. Due to high moisture and sugar content, it is very susceptible to microbial growth and spoilage risk is high. Fruit juices and drinks containing fruit juices are prone to spoilage by spore-forming bacterium are either fresh (not heat-treated) or pasteurized (but not UHT-treated) and stored unpreserved at ambient temperatures (Pettipher et al., 1997). So, producers need to add preservatives and requires the thermal destruction of microorganisms. Thermal processing may cause the deterioration of heat sensitive nutrients and volatile components and sometimes produce undesirable compounds. Different processing and preservation techniques, such as drying, special packaging, and chemical treatments are used to preserve the fruit juice. Among all preservation methods drying of fruit juice in the powder is a unique technique which increases the shelf life of fruit juice (Chen and Mujumdar, 2009; Kha et al., 2010; Quek et al., 2007). In powder form, moisture content is at microbiologically safe levels, as the water activity becomes very low. There are different types of drying methods available. The most common, convenient and widely practiced method is spray drying to prepare fruit powder (Fernandes et al., 2011; Phisut, 2012). Fruit powder is used to produce cake, candy as well as refreshment drink.

Fruit powder is amorphous dry granular material and is highly hygroscopic in nature. Therefore, careful handling and special packaging is required during marketing, transportation and storage. It is bulky in nature as well. Hence, more space is required for transportation and storage. However, alternative techniques such as compaction of fruit powder in the shape of tablets is more suitable to overcome the post processing problems regarding storage, transportation, and quality degradation. Tableting results in the reduction of surface area and bulk volume of the powder. The advantages of tableting includes good chemical and physical stability, prolonged shelf life, and competitive unit production cost, as well as reduction in transportation and storage cost, elegant appearance and greater acceptance in terms of presentation (Yusof et al., 2012). Normally, people take fruit powder tablets either in juice form after dissolving it in

water or as candy. Hence, fast dissolving fruit powder tablets will be more acceptable to consumers. However, the major drawback of fruit powder tablets is poor dissolution rate. To make the tablets dissolve fast, super dis-integrants or effervescent agents are used with fruit powder during tableting (Ong et al., 2014; Zea et al., 2013).

Figure 1.1: Plum fruit candy tablet available in market

Dissolution is a physicochemical process, in which a solute and solvent mix together to produce a uniform mixture. It is very important for the dry and powder food products which are used in liquid or gel/semisolid form. Hence, dissolution rate is a crucial factor for dry foodstuff. Dissolution rate depends upon its physical properties and chemical composition. It also depends on the physical state of material. In the food sector, this test usually used to measure the solubility of powder foodstuff such as food hydrocolloid powder, milk powder, and fruit powder. It is also used for compressed fruit powder such as tablet; for checking total disintegration time, antioxidant release (Adiba et al., 2011). Dissolution testing for tablets is a formal test in pharmaceutical and nutraceutical industries. It is typically used to check the quality of the product, develop new products, and determine the bioavailability of the drug after dissolution (Costa and Lobo, 2001; Dash et al., 2010; Dressman et al., 1998). Dissolution rate of a tablet depends upon the type of ingredients it contains. It may be hydrophilic, moderately hydrophilic, or hydrophobic. The Center for Drug Evaluation and Research at the US Food and Drug Administration (FDA, 1997a) reported three types of dissolution test specification for immediate release products; (1) single point specifications; (2) two-point specifications; and (3) dissolution profile comparison. Among these, the dissolution profile comparison is a more precise technique to specify the product (Sathe et al., 1996; Shah et al., 1998). The methods for comparison of In-vitro dissolution profile may be divided into three groups: (1) Model-dependent method, (Dash et al., 2010; Polli et al., 1997; Sathe et al., 1996; Shah et al., 1992); (2) Model-independent methods (Costa & Lobo, 2001; Dash et al., 2010; Polli et al., 1997; Shah et al., 1992); and (3) Statistical methods (Analysis of variance (ANOVA) based method or *t*-student test) (Costa & Lobo, 2001; Dash et al., 2010; Mauger et al., 1986; Polli et al., 1997). For pharmaceuticals, tablet dissolution performance is measured based on release rate of active pharmaceutical ingredients (API) or drug.

1.2 Problem statement

The demand of ready-to-eat or ready-to-serve foods and drinks is increasing day-by-day. Tableting of fruit powder into ready-to-drink juice tablet/fruit candy is able to meet consumer demands. However, acceptability and popularity of the fruit powder tablets depends on dissolution behavior and dissolution rate. Most fruit powders are sticky in nature due presence of low molecular weight of sugar. To overcome stickiness and increase the glass transition temperature (Tg), a necessary amount of high molecular weight carrier agents must be used during powder production, which able to alter the physicochemical properties and solubility/wettability of powder (Grabowski et al., 2006). The physicochemical properties of powder have a strong influence on compressibility and tableting behavior of fruit powder, which affect the dissolution characteristics of finish products as well.

Dissolution test of fruit powder tablets is vital from the point of large scale production and quality checking of finished products. In-vitro dissolution tests are usually used to: (1) assess the batch-to-batch quality of product; (2) develop new formulations and (3) ensure continued product quality and performance after certain changes, such as changes in the formulation, manufacturing process, the site of manufacture, and the scale-up of the manufacturing process. These are done using dissolution profiling and profile comparison (Yuksel et al., 2000).

From the literature it is clear that although fruit powder effervescent tablets are more beneficial than other products, they are typically not available in local markets. Therefore, based on the demands and benefits of fruit powder tablets, there is a need for large scale production. For large scale production, physicochemical properties of powder are very important in terms of storage, transportation, handling, processing, and quality of finished product as well. Besides, dissolution information of the fruit powder tablets is also very essential for quality control/checking, product development, and scale up in production capacity.

1.3 Objectives

The main objectives of this study are as follows:

1. To investigate the physicochemical properties of fruit powder and their effects on dissolution rate of fruit powder tablets.
2. To investigate dissolution profiling for natural fruit powder fast dissolve tablet and comparison of dissolution profile of natural fruit powder fast-dissolve tablets.

1.4 Scope of study

The physicochemical properties of powder material are of particular importance to food processor and consumer in terms of production and dissolution of fruit powder tablet. Tableting of fruit powder is a special technique of fruit powder preservation and product development. Tablet quality depends on its ingredients' properties, while the suitability of tablet depends upon dissolution behavior and dissolution rate.

Effervescent agents also affect the dissolution characteristics. Literature shows most of the research about fruit powder production, yield, different effects on nutritional quality, drying methods and nutritional properties of fruit powder. However, very limited research may be found in post-processing handling, transportation, storage, preservation and solubility. Therefore, there is room for research about physicochemical properties of fruit powder and their relationship in fruit powder tablet dissolution, dissolution profiling and its comparison for quality control, and large scale production of tablets.

Dissolution rate and behavior of fruit powder tablet differ in different dissolution mediums and environments. In this study, two types of dissolution medium, namely, distilled water and simulated saliva, have been used, as people usually take a fruit powder tablet in juice form after dissolving in water or directly as like candy. The dissolution profile of fruit powder tablets represent the relationship between percent amounts of tablet dissolved and percent solute release from the tablet versus time. Dissolution profiling and profile comparisons of fruit powder tablet are very important in terms of characterization of product, quality control, and scaling up the process. Three types of method are usually used for profile comparison such as model dependent, model independent and statistical method. However, physicochemical properties of fruit powder tablet have a great influence on dissolution rate and behavior of fruit powder tablet and which also affect dissolution profile. Yet, the model based dissolution profile comparison methods does not consider chemical properties of tablet ingredients. The models have been established based on some mathematical metaphor of some aspects of reality and considering physical feature of tablets. Therefore, in this study three types of methods have been used for dissolution profile comparison.

1.5 Organization of the thesis

Chapter 1 contains a general introduction to the thesis. The overview of this research, problem statement, objectives scope of study, and organization of the thesis are also presented.

Chapter 2 discusses and reviews in detail the physicochemical properties of food powder, tablet, tableting method, effervescent tablet, dissolution of tablet, dissolution profiling of tablet, dissolution profile comparison, dissolution kinetics mathematical model, and selection criteria of best fit mathematical model.

Chapter 3 reports all the materials and experimental procedures involved in performing this research. Proximate analysis of fruit powders, physical properties of fruit powder, dissolution test, data collection, and data analysis are described.

Chapter 4 report and discusses on physicochemical properties of fruit powder, dissolution profile of effervescent fruit powder tablet, best fit mathematical model with the dissolution data of fruit powder effervescent tablet. The comparison of, dissolution profile of fruit powder effervescent tablets are performed based on model dependent, model-independent and statistical method.

A brief summary on all study and findings are presented in **chapter 5**. The recommendations for future study are given in this final chapter.

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