Original Article

Preparation and evaluation of a new fast dissolving oral film containing Matricaria Chamomilla extract to antisepticising Oral cavity

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Abstract

Many patients suffer from oral cavity infections and there is a relation between periodontal infections and systemic diseases. The extracts of medicinal plants are used directly or indirectly for the treatment of many diseases. *Matricaria Chamomilla* is a well-known medicinal herb used as an antimicrobial and antiviral agent, so that it can use to antisepticising oral cavity. Fast dissolving oral films (FDOF) are solid dosage forms, which the consumer can take without water or chewing and disintegrate within a few seconds in the mouth and release their ingredients. The aim of this study is the preparation and evaluation of a new FDOF containing *Matricaria Chamomilla* hydroalcoholic extract to antisepticising oral cavity. In this study, FDOFs containing *Matricaria Chamomilla* extract were made with polyvinyl alcohol and gelatin as the base polymers, and glycerin as the plasticizer by the casting method. The prepared FDOFs were evaluated for pharmaceutical properties such as surface uniformity, physical appearance (visibility, absence of air bubbles, fractures, cracks and shrinkage), flexibility, disintegration time and dissolution time. Design-Expert 11.0.3.0 (Stat-Ease, Inc., Minneapolis, USA) was used to design and optimize formulations using a random quadratic optimization model. Evaluation of the films showed that the formulation containing polyvinyl alcohol and gelatin as polymer and glycerol as plasticizer had desirable pharmaceutical properties and least disintegration and dissolution time, which ensures fast releasing of active substances. In this study a new FDOF Containing *Matricaria Chamomilla* extract was made. The formulated fast dissolving oral film stands as a promising dosage form for antisepticising oral cavity and Prevention of oral infections Instead of old mouthwashs.

Keywords: *Matricaria Chamomilla*, Fast-Dissolving, Oral Film, Oral Cavity

Introduction

Many patients suffer from oral cavity infections. About one in two adults in the United States suffer from viral, fungal and/or bacterial periodontal infections [1]. Viral infections can be very painful and annoying. Several clinical variants of fungal and bacterial diseases have been recognized in the oral cavity and bacterial infections are more common in the world [2, 3]. Some of the most common diseases of the oral cavity, caused by viruses, fungal or bacteries are: Herpes simplex virus infection, Herpes zoster virus infection, Herpangina, Human papillomavirus-associated oral lesions, Mumps, Oral lesions of leprosy, Syphilitic leukoplakia and Oral candidiasis [1, 2]. The relation between periodontal infection and systemic diseases is bi-directional, i.e., periodontal infection can cause adverse systemic outcomes and certain systemic diseases predispose a person to have periodontal disease [1].

The extracts of medicinal plants are used directly or indirectly for the treatment of many diseases. Scientists are trying to investigate the benefits of medicinal plants to assist the sufferings patients [3]. *Matricaria Chamomilla,* which has been called as *Matricaria recutita, Chamomilla recutita*, and/or *Chamomilum nobile* and is commonly known as *German chamomile* and *Roman chamomile* is a well-known medicinal herb from the Asteraceae family. This plant used as antimicrobial, antiviral and anti-inflammatory agent [4–6]. The main constituents of this plant include the terpenoids α-bisabolol and its oxides and azulenes, including chamazulene. *M. Chamomille*'s components are active against Candida strains, Herpes simplex virus, S. aureus, Poliovirus and more bacteria, viruses and fungal. So it is used as antiseptic agent in mouthwashes to treat the oral cavity infctions [7–9].

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How to cite this article: Rostami, A., Niazadeh, S., Naderi, H. Preparation and evaluation of a new fast dissolving oral film containing Matricaria Chamomilla extract to antisepticising Oral cavity. Arch Pharma Pract 2020;11(S4):70-4.

Fast dissolving oral films (FDOF) are solid dosage forms, which the consumer can take without water or chewing and disintegrate within a few seconds in the mouth. films release active ingredients immediately after uptake into oral cavity [10]. FDOFs are easy to administer and provide better patient compliance in the elderly, pediatric, mentally retarded, nauseated and uncooperative patients [11]. Salbutamol, nicotine, ondansetron, folic acid, zolmitriptan, dextromethorphan, and loratadine containing films are some examples of developed FDOFs [10, 12]. In some studies, herbal extracts such as Resveratrol and Curcumin used as FDOFs [13, 14]. Various polymers such as sodium carboxymethyl cellulose (NaCMC), polyvinyl alcohol (PVA), gelatin and starch, with various plasticizers such as glycerin and polyethylene glycol 400 (PEG) are used to produce FDOFs [15, 16]. Plasticizer is a vital ingredient of the fast dissolving films. Plasticizer helps to improve the flexibility of the strip and reduces the brittleness of the films [17]. Manufacturing methods of FDOFs are solvent casting, semisolid casting, hot melt extrusion, solid dispersion extrusion and rolling. In solvent casting method water soluble polymers are dissolved in water and the drug along with other excipients is dissolved in suitable solvent then both solutions are mixed and stirred and finally casted in to the Petri plate and let to dried [18]. Several experiments will be performed on the prepared films, such as surface uniformity, physical appearance (visibility, absence of air bubbles, fractures, cracks and shrinkage), flexibility, disintegration time and dissolution time [18, 19]. The aim of this study is preparation and evaluation of a new FDOF containing *Matricaria Chamomilla* extract to antisepticising the oral cavity.

METHODS

Materials and Devices

To make the films, standard chamomile extract (based on the presence of 0.09-0.17 mg of chamazulene per milliliter) manufactured by Barij Essence Pharmaceutical Company was used, and PVA, gelatin and Glycerin manufactured by Merck KGaA have been supplied from the domestic market. A digital micrometer (model GB / T14899-94, China) was used to determine thickness of the films and a shaking water bath (Orbital Type/KBLee2020) was used to determine In vitro disintegration and dissolution Time. Design-Expert 11.0.3.0 (Stat-Ease, Inc., Minneapolis, USA) was used to design and optimize formulations.

Designing and optimizing formulations

To find best polymers and Plasticizer to continue the study, Based on the results of previous studies [10, 15, 16], NaCMC, PVA, gelatin and starch as base polymers and glycerin and PEG as plasticizers was selected. Initially, 12 formulations were designed using two polymers (2:2 ratio in pairs) and one plasticizer with a ratio of one. To confirm the results, three samples from each formulation were made (finally 36 films). Pharmaceutical properties such as surface uniformity, physical appearance and flexibility were reviewed. Based on results (reported in table 2) PVA, Gelatine and Glycerine was selected to continue the study.

after selecting polymers and plasticizer, to obtain the best results, Design-Expert was used to design and optimize formulations using a random quadratic optimization model [20]. The design was validated using numerical point prediction optimization method in software. (18 formulations including 14 unique and different formulations and 4 checkpoints)(Table 1). To confirm the results, three samples from each formulation were made. After analyzing the data, Design-Expert software delivers the final result with a parameter called the desirability factor. Due to the higher desirability factor was determined by Design-Expert software in the proposed limitations (shortest disintegration time and dissolution time), optimal formulation was selected.

Table 1. The amount of each polymer and plasticizer in a desired size of cutted films in 18 formulations

Formulation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
PVA (mg)	50	0	33.3	40	50	50	90	0	30	100	80	100	55	0	0	40	0	0
Gelatin (mg)	0	50	33.3	0	50	0	0	40	30	0	0	0	15	50	100	40	80	100
Glycerin (mg)	0	0	0	20	0	0	10	20	10	0	20	0	15	0	0	20	20	0

Preparation the FDOFs

In this study, the solvent casting method was used for preparation the films. In this method water soluble polymers (PVA and gelatin) and plasticizer (glycerin) were dissolved in water on heater-stirer device and lastly other exepients and active substance added. The mixture was stirred to form homogeneous solution. The resulting solution was poured into a circular plate with an area of 40 cm2 as a film and allowed to dry in a fan oven at 40 ° C for 48 hours. The obtained film cut into pieces of the desired size of 4 cm2. *Matricaria Chamomilla's* extract was present in all the films created [11, 21, 22].

Evaluation the films

Pharmaceutical properties such as surface uniformity, physical appearance (visibility, absence of air bubbles, fractures, cracks and shrinkage), flexibility, disintegration time and dissolution time were evaluated for the films.

Surface uniformity of the films is directly related to the uniformity of the amount of drug presented in various portions, so, to equalize the film thickness, before placing the plate in the oven for drying, the oven floor was adjusted so that it would not slope in any direction [10, 23]. To ensure uniformity, thickness of the films was measured at least at

five different points (one point in the center and one point on each side) using a digital micrometer with a sensitivity of 0.01 micrometer. If the thickness difference in measured points is less than 5%, the films are uniform in thickness. Results were expressed as two levels of Score 1: unacceptable and Score 2: acceptable. The formulations that led to the production of unacceptable films were excluded from the study [10].

The physical appearance of the films (visibility, absence of air bubbles, fractures, cracks and shrinkage) was observed. The result of the evaluation of the physical appearance of the films were expressed as two levels of Score 1: unacceptable and Score 2: acceptable. The formulations that led to the production of unacceptable films were excluded from the study [10, 19]. To evaluat flexibility, the films were folded in a specific axis to make it clear how many times they would break. The films should not be too dry and brittle and not too soft and sticky. Films that were broken after 3 to 6 folds were selected as acceptable, and films that were broken by less than 3 folds or not broken by more than 6 folds were considered unacceptable. Results were expressed as two levels of Score 1: unacceptable and Score 2: acceptable. The formulations that led to the production of unacceptable films were excluded from the study [10]. Each formulation received a score of one or two in each of the above three evaluations. From each formulation, three samples were made. Therefore, each formulation had a score from 9 to 18. This ranking was used to select formulations with appropriate pharmaceutical properties.

In vitro disintegration time is the time when the film begins to crack, crumble or break down (Fiqure 1). This parameter was visually determined using a timer; the cut films were immersed in a glass dish containing 25 ml of distilled water on a shaking bath, at a rotational speed of 50 rpm at 37±0.5° C. Then, The time of cracking, crumbling or breaking down was recorded as the disintegration time [22, 24].

Figure 1. A film in disintegration time

In vitro dissolution time is the time when the film dissolved completely. The shorter the dissolution time, the sooner the drug is released from the film and spread into the oral cavity. Dissolution time determined using a timer; the cut films were immersed in a glass dish containing 25 ml of pH 6.4 phosphate buffer on a shaking bath, at a rotational speed of 50 rpm at 37±0.5° C [22].

Results and Discussion

For the 12 formulations made using two polymers (2:2 ratio in pairs) and one plasticizer with a ratio of one, surface uniformity, physical appearance and flexibility were evaluated, Sum of the scores of each film are reported in table 2.

Table 2. The score of each formulation, based on three samples of each formulation and evaluation of three tests (surface uniformity, physical appearance and flexibility) (each test: 0-2 Score); (max: 3*3*2=18)

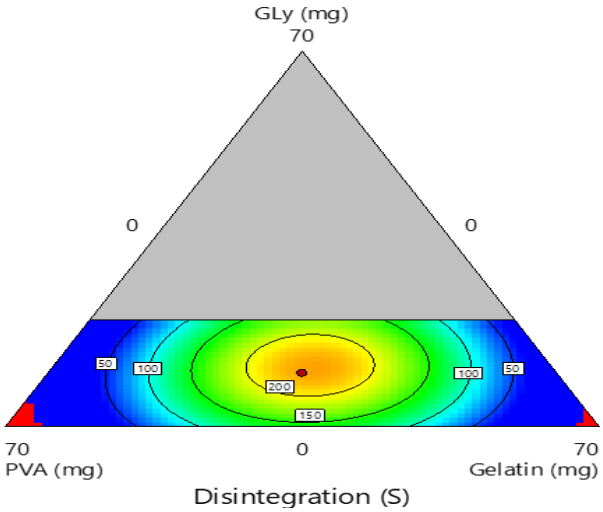
Formulations	PVA NaCMC	PVA Gelatin	PVA Starch	NaCMC Gelatin	NaCMC Starch	Gelatin Starch
Glycerin	15	18	15	16	14	16
PEG 400	15	16	15	15	13	15

Existence of PVA and Gelatin together, led to the production of very uniform and appearant films. existence of PEG in the formulation, led to the production of very soft and overly flexible films, but the glycerin had a good result. So, Evaluation of these films showed that all films made of PVA, gelatin and glycerol have the best pharmaceutical properties such as surface uniformity, physical appearance and flexibility. Therefore, based on the highest score obtained, this combination was selected to continue the study. To obtain the best results in fast-dissolving, Design-Expert software was used to design formulations and disintegration time and dissulution time was calculated for films (table 3)

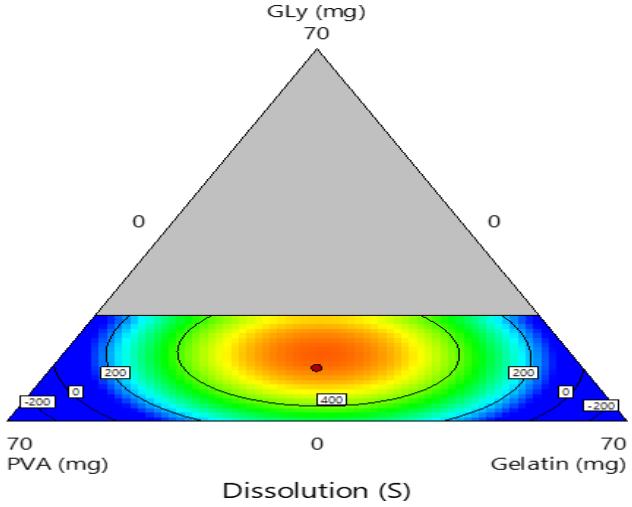
Table 3. Disintegration time and dissolution time for 18 formulation designed by Design-Expert software

Formulation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Disintegration time (S)	40	51	154	43	146	42	168	81	221	130	126	118	121	48	110	257	101	116
Dissolution time (S)	185	271	335	122	540	189	402	139	543	352	375	356	430	259	309	601	234	318

Based on the results, as shown in Figures 2 and 3; Film production is not possible without the use of polymers. Using a single polymer alone is good, but the results of visual examinations will not be as good when two polymers are combined with the presence of a plasticizer.



Fiqure 2. effect of 3 component of formulation on disintegration time.



Fiqure 3. Effect of 3 component of formulation on dissolution time.

Considering the importance of less time for disintegration and dissolution of films while having two polymers and a plasticizer in the formulation, the software proposed the following formulation as the optimal formula with a degree of desirability of 1 out of 1. According to the software outputs, disintegratin time and dissolution time, for the formulation containing 552.7 mg of PVA, 91.3 mg of gelatin and 44.4 mg of glycerin with a certain amount of chamomile extract, will be equal to 43.5 and 121.4 seconds, respectively. The results will be very good in terms of speed of disintegration and dissolution, if they actually happen. To ensure this, 9 of these formulation were produced and evaluated, and the results were presented in table 4. Each formulation received a score of one or two in each of this evaluations: surface uniformity, physical appearance and flexibility, and disintegration and dissolution times are reporetd.

Table 4. The score of 9 samples of final formulation, based on three tests (surface uniformity, physical appearance and flexibility) (max: 6) and their disintegration and dissolution times.

Sample number	1	2	3	4	5	6	7	8	9
Score	6	6	6	6	6	6	6	6	6
Disintegration time (S)	50	46	43	49	51	45	44	42	49
Dissolution time (S)	132	129	136	125	131	130	128	127	124

As shown in the initial studies, the combination of the two selected polymers and plasticizer showed acceptable physical and physical properties. According to the forecast, the disintegration time of final formulation should be 43.5 seconds and In examining the samples, this value was 46.55 seconds on average. In fact, the final result was 7% different from the predicted result. On the other hand, the dissolution time of final formulation should be 121.4 seconds and In examining the samples, this value was 129.11 seconds on average. In fact, the final result was 6.3% different from the predicted result. Therefore, considering that the results of making the samples are acceptable in terms of research objectives, based on the fast dissolability, the formulation proposed by the software was accepted as acceptable formulation.

Conclusion

The extract of *Matricaria Chamomilla* is used directly or indirectly for the treatment of many diseases. One of the dosage forms that can be used to consume chamomile extract is fast dissolving films. In this study a new FDOF Containing *Matricaria Chamomilla* extract was made by formulation containing PVA and gelatin as polymers and glycerin as plasticizer. The formulated fast dissolving oral film stands as a promising dosage form for antisepticising oral cavity and Prevention of oral infections Instead of old mouthwashs. We suggest that in further research, Other Specification of this films such as surface pH, tensile strength, elongation percent, Folding endurance and in-vitro and in-vivo anticepticizing function be assessed.

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