Original Article

Trends in Pharmaceutical Sciences 2015; 1(1): 25-30

Development and in vitro evaluation of fast-dissolving oral films of ondansetron hydrochloride

Shohreh Alipour[1], Sahar Akbari[1], Fatemeh Ahmadi[2*]

[1]Pharmacy Department, International Branch, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Department of Pharmaceutics, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

Abstract

Ondansetron hydrochloride, a selective 5-HT3 receptor blocker, is an effective antiemetic drug with oral bioavailability of 60% and half-life of 4-5 hours. The present study was carried out to prepare fast dissolving films of ondansetron hydrochloride to increase patient compliance and improve efficacy of this drug. Films were prepared by solvent casting method, using poly vinyl alcohol, poly vinyl pyrrolidone and konjac glucomannan as film formers and PEG400 as plasticizer. Natural and synthetic sweeteners were used for masking bitterness of the drug. Satisfactory results were obtained from evaluation of physical characteristics of fast dissolving films of ondansetron hydrochloride including: thickness (0.37-0.39 mm), surface pH (6.77), folding endurance (up to 300 times) and tensile strength (35.75-50.93 g/cm²). Films were also subjected to an in vitro dissolution and release studies. In vitro drug release studies indicated 93-95% release in 5 min. Fast dissolving films of ondansetron could be a potential alternative for the currently marketed oral formulation, parenteral form and suppository with better patient compliance and higher bioavailability for the rapid control of emesis.

Keywords: Fast dissolving film, Konjac glucomannan, Ondansetron, Poly vinyl alcohol, Solvent casting.

1. Introduction

Patient compliance is a major challenge in chemotherapy regimens. Patients receiving chemotherapy agents always complain of nausea and vomiting caused by these drugs. Ondansetron hydrochloride, a 5-HT3 antagonist, with inhibiting serotonin receptors is effective against nausea and vomiting especially the nausea and vomiting associated with chemotherapy regimens (1,2). Currently, marketed dosage forms of ondansetron include oral tablets, suppositories and injection. Data of pharmacokinetic studies show that despite rapid absorption of the drug following oral administration, it is quickly metabolized by the liver. First pass effect causes the bioavailability of the drug to be 60-70%. The half-life of the drug is also relatively short (3). Although parenteral administration of ondansetron provides immediate effects, it can cause some side effects such as headache, constipation or diarrhea. Indeed, with rectal administration of drugs, there is always risk of leaking out of the rectum, low patient compliance and relatively slow absorption (4).

Development and manufacture of new dosage forms to improve patient compliance and quality of life has been increased in recent decades. Feasibility of using oral solid dosage forms is the major issue in some populations of patients like pediatrics, geriatrics, patients with nausea and vomiting or swallowing problems (5,6). Fast dissolving oral dosage forms were introduced in the late 1970s to facilitate use of drug for disabled patients and to develop rapid drug delivery systems (6). Because of unique features such as quick disintegration and fast dissolution time as well as administration without water, fast dissolving delivery systems are very attractive for geriatric and pediatric patients (1,7). Fast dissolving dosage forms include oral disintegrating tablets (ODTs) and oral disintegrating films (ODFs) which are rapidly disintegrated and dissolved in mouth without need to water or chewing (8). ODTs are a new class of tablets which are rapidly disintegrated in the mouth and can be used for buccal

Corresponding Author: Fatemeh Ahmadi
Department of Pharmaceutics, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran
E-mail: ahmadi_f@sums.ac.ir

Received: 11/03/2014; Accepted: 09/07/2014

or sublingual delivery. Since taking these tablets is easier, they have become popular and are accepted as an alternative for traditional simple tablets.

ODFs are oral strips made from hydrophilic polymers containing active substance and excipients. These films are rapidly disintegrated when come in contact with saliva and release the drug immediately afterwards (3,9). Compared to tablets, ODFs present some advantages such as no risk of suffocation and choking (5), simple fabrication and cheaper manufacturing process (9,10) as well as flexibility and higher chance for patentability (11).

The advantages of ODFs mainly include fast dissolving without the need of water, rapid absorption from the highly vascularized oral mucosa and bypassing first pass metabolism which makes them a suitable system for administration of ondansetron to patients with emesis. Therefore, our aim was to develop a fast dissolving oral film of ondansetron hydrochloride to improve efficacy of drug and increase patient compliance. The films were prepared by solvent casting method and their tensile strength, flexibility, drug content and dissolution time were examined by relevant *in vitro* tests.

2. Materials and methods

Ondansetron hydrochloride was obtained from Exir Pharmaceutical Company (Borujerd, Iran). Poly vinyl alcohol (PVA), poly vinyl pyrrolidone (PVP), sodium alginate, microcrystalline cellulose (MCC), NaCMC, HPMC, aspartame, sorbitol, mannitol, sodium saccharin, acesulfame, citric acid, PEG 400 and glycerol were purchased from Merck (Darmstadt, Germany). Konjac glucomannan (KG) was obtained from Richest Group Company (China). Strawberry, mint and lemon essential oils were purchased from local supplier, all other chemicals and solvents were of analytical grade.

2.1. Preparation of ondansetron hydrochloride films

PVA, PVP, NaCMC, HPMC, sodium alginate, MCC and KG were used as film formers. PEG 400 and glycerol as plasticizer, sodium saccharin, mannitol, sorbitol, aspartame and acesulfame as sweetening agents and strawberry, lemon and mint essential oils as flavoring agents were used in different formulations.

The films were prepared by solvent casting method. Film forming polymers were dissolved in 20 ml of hot water and stirred vigorously to obtain a clear solution (solution I). One hundred mg ondansetron HCl was dissolved in 10 ml distilled water containing 5% plasticizer (solution II). Then solution I and solution II were mixed and the final solution was allowed to stand overnight at room temperature to remove the air bubbles. Then, 7 ml of the solution was poured into a petri dish. The petri dishes were kept in vacuum desiccator until completely dried. The films were then carefully removed and examined for any imperfection. The resulting films were cut into squares with dimension of 2.5×2.5 cm². In this way, each square contained 4 mg of the active ingredient. Combination of PVA, PVP and KG provided the most suitable film formulations; therefore, 13 final formulations were prepared using these polymers. The composition of the final formulations is illustrated in Table 1.

2.2. Determination of weight and thickness

Weight variation of 10 films was evaluated by a digital balance (Sartorius, Germany). Thickness of each sample was measured using a caliper and the mean thickness was calculated.

2.3. Surface pH

The surface pH of films was determined in order to prevent the risk of side effects presented by extreme pH values. Since acidic and alkaline pH can cause irritation in oral mucosa, surface pH should be kept close to neutral. Samples were placed in petri dish and then 1 ml of distilled water was added to each sample. After 30 min, pH of the resulting solution was determined by means of a digital pH meter. The measurement was repeated for 3 films of each formulation.

2.4. Testing of folding endurance

Folding endurance was defined as "the number of times that a piece of film could be folded at the same point, without breaking". This test was used to determine the degree of films fragility or flexibility (12).

2.5. Determination of tensile strength of films

The mechanical properties of films were evaluated using a texture analyzer (model CT3, Brookfield, USA) with a 1-kg load cell. Film strips in constant dimension (5 cm x 1 cm) and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 4 cm. During measurement, the strips were pulled by the upper clamp at a rate of 0.2 mm/s. The force and elongation were measured when the film was broken. Measurements were run in triplicate for each formulation. Two mechanical properties, tensile strength (TS) and the percentage of elongation were computed for the evaluation of the films. TS is the maximum stress applied at the point that the film specimen is broken and can be calculated by the ratio of force at break to cross-sectional area of the specimen. The percent of elongation is the ratio of increase in length at break to the original length (2,13).

2.6. FT-IR spectroscopy

The compatibility of drug and excipients in the formulations was confirmed by FT-IR spectroscopy. Spectra of pure drug and formulations were recorded using a Bruker FTIR-Vertex 70 Spectrophotometer.

Table 1. Composition of the final films of ondansetron hydrochloride.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Ondansetron (mg)	100	100	100	100	100	100	100	100	100	100	100	100	100
PVA (mg)	240	240	270	270	270	150	240	270	300	300	300	300	300
PVP (mg)	60	60	30	30	30	—	—	—	—	—	—	—	—
KG (mg)	—	—	—	—	—	150	60	30	75	150	150	150	150
Glycerol (ml)	—	0.15	—	—	0.15	—	—	—	—	—	—	—	0.15
PEG400 (ml)	0.5	0.35	0.5	0.5	0.35	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.35
Citric acid (mg)	100	100	100	100	100	100	100	100	100	100	100	100	100
Mannitol (mg)	—	—	40	20	—	—	—	—	—	—	20	20	—
Sorbitol (mg)	—	—	—	—	—	—	—	—	—	40	—	—	—
Na-Saccharin (mg)	—	—	1	—	—	—	—	—	—	1	—	—	—
Aspartame (mg)	—	—	—	20	35	—	—	—	—	—	20	—	35
Acesulfame (mg)	—	—	—	—	—	—	—	—	—	—	—	20	—

2.7. Taste masking studies

The film formulations with the most suitable physical characteristics were selected for taste masking studies. One ml of each of flavoring agents (strawberry, mint and lemon oil) were separately added to each selected formulation. The efficacy of sweetening and flavoring agents for masking the bitter taste of ondansetron was evaluated by volunteers. Eighteen healthy adult volunteers tested the formulations and ranked the masking ability of sweetening and flavoring agents as weak (-), fair (±), good (+) and very good (++).

2.8. Drug content uniformity

One piece of 2.5×2.5 cm^2 of the film with nominal content of 4 mg ondansetron hydrochloride was dissolved in 100 ml of simulated saliva pH 6.8 (phosphate buffer with NaCl) for 30 min by continuous shaking to obtain a homogeneous solution. Then, 10 ml of this solution was diluted to 50 ml with simulated salivary fluid. The absorbance was measured at 310 nm using UV Spectrophotometer (Shimadzu, Japan). The experiment was performed three times for the films of all formulations.

2.9. In vitro dissolution studies

In vitro dissolution study of fast dissolving films of ondansetron hydrochloride was performed using USP type II (paddle apparatus) in 500 ml simulated salivary fluid (pH 6.8). Dissolution media was kept at 37.5±0.5°C and paddle rotating rate was set to 100 rpm. Every 30 sec, 5 ml of samples were withdrawn, and replaced with the same amount of fresh medium. UV absorbance of samples was read at 310 nm and the percentage of drug released was plotted against time.

3. Results and discussion

3.1. Preparation of ondansetron fast dissolving films

Fast dissolving oral films should be very soluble in water to release their content in a short time. A series of hydrophilic polymers were examined for preparation of ondansetron fast dissolving films. Four criteria were considered for selecting the most suitable polymer for film preparation. These criteria were film-forming ability, elasticity, flexibility and removability from the surface. MCC is not a good film forming polymer and it should be mixed with other polymers to provide fast dissolving properties (14,15). Besides, alginate films were very brittle and properties of this polymer should also be modified by mixing with other polymers (16). Formulations containing NaCMC were very brittle and could not be removed from the surface. Similar studies report that casting of NaCMC films from ethanol or mixture of water and ethanol would provide better results (15,16). HPMC films were transparent

Table 2. Taste masking ability of different sweetening agents used in formulations.

Formulation	Sweetening effect
F3	+
F4	-
F5	++
F10	+
F11	-
F12	-
F13	++

Table 3. Physical characteristics of ondansetron films (n=3).

Film characteristic	F5	F13
Drug content (mg)	3.89±0.17	4.03±0.09
Thickness (mm)	0.37±0.01	0.39±0.01
Folding endurance	>300	>300
Surface pH	6.46±0.04	6.65±0.06
Weight (mg)	55.56±2.87	71.56±1.40

and easily removable from the surface, but they lacked flexibility and elasticity. It has been observed for HPMC films of montelukast sodium and rofecoxib that 3-4% of polymer is required to obtain a suitable film (7,17). Results showed that PVA provided films with a better quality and it was chosen for preparation of final formulations. PVA in concentration ranges of, 1-3% can provide fast dissolving films with suitable physical properties (18). The film characteristics could also be modified by mixing with other polymers (2, 3,18). Therefore, mixtures of PVA with PVP and KG were evaluated for film forming in next formulations. Formulations F3, F4, F5, F10, F11, F12 and F13 presented the most suitable films. These formulations were used for taste masking studies as seen in Table 1. All films prepared from these formulations, were almost transparent and flexible with a smooth surface. Increasing the percent of PVP in the films prepared from PVA and PVP mixture reduced the elasticity of polymer. KG is a natural biodegradable film forming agent which can form films with higher stability and elasticity through hydrogen bonding (19).

Different combinations of sweetening agents were tested to find the best tasting formulation. Results of evaluating the sweet taste of formulations by healthy volunteers are presented in Table 2. Sodium saccharin in combination with mannitol or sorbitol could mask the bitterness of drug, but bitter aftertaste

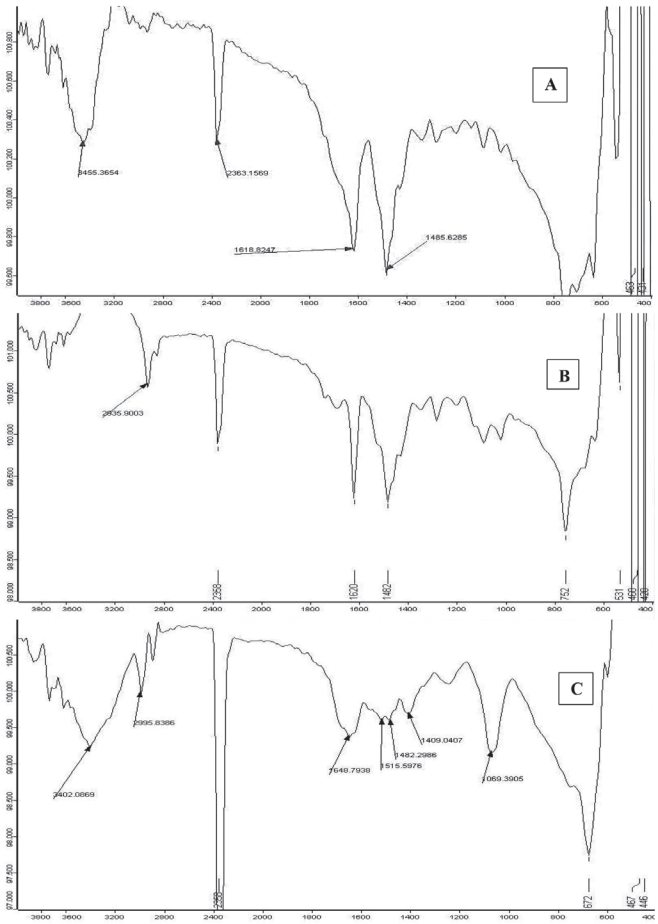

Figure 1. FT-IR of (A) ondansetron, (B) F5 and (C) F13.

Table 4. Results of determination of tensile strength of ondansetron films (n=3).

Formulation	Tensile Strength (g/cm²)	Peak Load (g)	Elongation at Break (cm)	Work (mJ)
F5	50.93±16.03	101.86 ± 32.06	3.11±0.83	24.06±13.84
F13	35.75±6.03	71.50±12.06	0.30±0.05	1.72±0.67

was still a problem. Acesulfame was not compatible with other ingredients of the formulation and caused aggregation of the film. Based on volunteers' opinion, aspartame was selected as the most suitable sweetener for masking the bitter taste of ondansetron. F5 and F13 were selected as the optimum formulations of the mixture of PVA/PVP and PVP/KG, respectively. Effect of different flavoring agents on the taste of selected formulations was also investigated and the results showed that strawberry oil was not acceptable by any of the volunteers. The taste of lemon oil was very acceptable for all volunteers and the mint oil taste was moderately acceptable. Thus lemon oil was chosen as the optimum flavoring agent. Based on the film forming results and taste masking ability, formulations F5 and F13 which contained aspartame were selected for further studies. Lemon oil was also added to these formulations as flavoring agent.

3.2. Characterization of films

Results of physical characterization of films are presented in Table 3. As implied from the date, selected formulations were uniform in thickness and drug content. The results of evaluation of surface pH showed that the pH level of formulations were near neutral. This shows that probability to irritate the oral mucosa is essentially low.

Folding endurance more than 300 in formulations indicates that they were flexible and tough. The designed films, with regards to their physical properties, were very similar to the films of ondansetron developed by Koland et al. (2,3).

Tensile strength testing was used to evaluate the strength and elasticity of films. Two parameters were defined; tensile strength (TS) and elongation at break (E/B). The tensile strength and E/B were greater for F5 which was consisted of PVA and PVP. Generally, a weak and soft polymer presents a low TS and E/B; while a hard and brittle polymer is characterized by a moderate TS and low E/B. Indeed, a soft and tough polymer shows a moderate TS and high E/B whereas a hard tough polymer presents a high TS and E/B (2,3). Therefore, formulation F5 is tough and strong enough for use. Table 4 shows the results of measuring tensile strength of films.

3.3. FT-IR spectroscopy

The results of IR studies in Figure 1 indicates that there was no interaction between drug and the polymer used in formulations. The characteristic peaks of ondansetron (carbonyl and N-H) are still observed in IR spectra of formulations.

3.4. In vitro dissolution studies

In vitro drug release studies using USP type II (paddle apparatus) revealed that formulation F5 released 95% of the drug content in 5 min and for formulation F13 this value was 93% of the drug content. Release profiles in Figure 2 prove rapid dissolution and hence fast drug release of these film formulations. A dissolution time of 5 min is very desirable for a fast dissolving film of an antiemetic

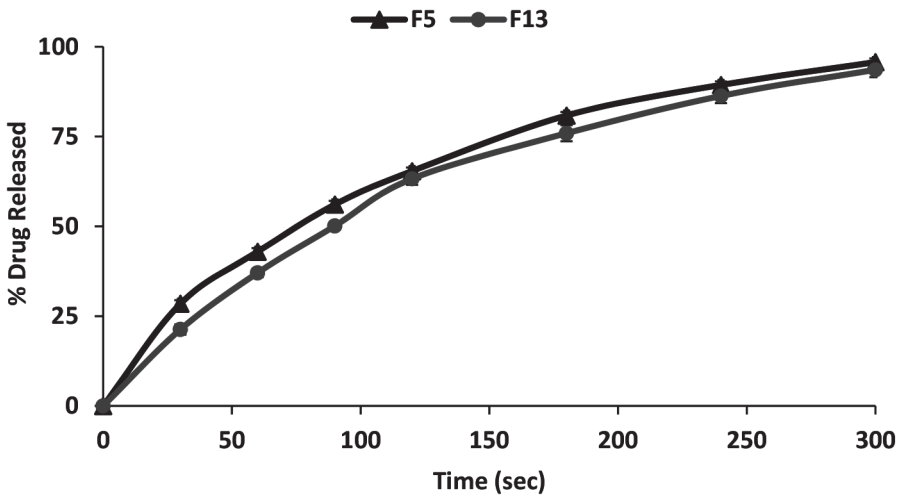

Figure 2. *In vitro* release profiles of films of formulation F5 and F13 in simulated saliva (n=3).

agent. The results are in accordance with the previous studies on ondansetron films (2,3).

4. Conclusion

Fast dissolving films of ondansetron hydrochloride were developed using water soluble polymers such as PVA, PVP and konjac glucomannan as film formers and PEG 400 and glycerol as plasticizers.

The ODFs showed appropriate physical characteristics (i.e. flexibility, acceptable surface pH, folding endurance, tensile strength and thickness) and in vitro release profile. It seems that ODFs can be used as a suitable alternative for the marketed oral dosage form of ondansetron providing better patient cooperation, higher bioavailability and faster action.

5. Acknowledgments

The present article was extracted from a Pharm. D. thesis written by Sahar Akbari and was financially supported by Shiraz University of Medical Sciences, International Branch.

Conflict of Interest

None declared.

6. References

1. Choudhary DR, Patel VA, Chhalotiya UK, Patel HV, Kundawala AJ. Natural polysaccharides as film former: A feasibility study for development of rapid dissolving films of ondansetron hydrochloride. Int J Pharm Pharmaceut Sci. 2012;4:78-85.
2. Koland M, Sandeep VP, Charyulu NR. Fast dissolving sublingual films of ondansetron hydrochloride: Effect of additives on invitro drug release and mucosal permeation. J Young Pharm. 2010;2:216-22.
3. Koland M, Sandeep VP, R. Charyulu NR, Subrahmanyam EVS. The design and characterisation of sublingual films of ondansetron hydrochloride. Int J Chem Sci. 2009;7:2927-38.
4. Dong-Min Park Y-KS, Jun-Pil J, Hyung Tae K, Chong-Kook K. Development of chitosan-based ondansetron buccal delivery system for the treatment of emesis. Drug Dev Ind Pharm. 2012;39:1077-83.
5. Arun Arya AC, Sharma V, Pathak K. Fast dissolving oral films: An innovative drug delivery system and dosage form. Int J ChemTech Res. 2010;2:576-83.
6. Bhyan B, Jangra S, Kaur M, Singh H. Orally fast dissolving films: Innovations in formulation and technology. Int J Pharm Sci Rev Res. 2011;9:50-57.
7. Ghorwade VAP, Patil S, Srikonda K, Kotagiri R, Patel P. Development and evaluation of fast-dissolving film of montelukast sodium. World J Med Pharm Biol Sci. 2011;1:6-12.
8. Cilurzo F, Cupone IE, Minghetti P, Selmin F, Montanari L. Fast dissolving films made of maltodextrins. Eur J Pharm Biopharm. 2008;70:895-900.
9. Panda BP, Rao MEB. Development of innovative orally fast disintrgrating film dosage forms. Int J Pharm Sci Nanotech. 2012;5:1666-74.
10. Parmar DUP, Bhimani B, Tripathi A, Daslaniya D, Patel G. Orally fast dissolving films as dominant dosage form for quick release. Int J Pharm Res Bio-Sci. 2012;1:27-41.
11. Dixit R, Puthli S. Oral strip technology: Overview and future potential. J Control Release. 2009;139:94-107.
12. Nehal Siddiqui GG, Sharma PK. A short review on "a novel approach in oral fast dissolving drug delivery system and their patents". Adv Biol Res. 2011;5:291-303.
13. Renuka Mishra AA. Manufacturing techniques of orally dissolving films. J Adv Pharm Technol Res. 2011;35:70-3.
14. Kulkarni A, Deokule H, Mane M, Ghadge D. Exploration of different polymers for use in the formulation of oral fast dissolving strips. J Curr Pharm Res. 2010;2:33-5.
15. Pathare YS, Hastak VS, Bajaj AN. Polymers used for fast disintegrating oral films: A review. Int J Pharm Sci Rev Res. 2013;21:169-178.
16. Podczeck F, Knight P, Newton J. The evaluation of modified microcrystalline cellulose for the preparation of pellets with high drug loading by extrusion/spheronization. Int J Pharm. 2008;350:145-54.
17. Kulkarni P, Dixit M, Gunashekara K, Shahnawaz A, Singh MN, Kulkarni A. Formulation and evaluation of mouth dissolving film containing rofecoxib. Int Res J of Pharm. 2011;2:273-8.
18. Mahajan A. Formulation and evaluation of fast dissolving buccal films of sertraline. Int J Drug Dev Res. 2012;4:220-6.
19. Zhang Y-q, Xie B-j, Gan X. Advance in the applications of konjac glucomannan and its derivatives. Carbohydrate Polym. 2005;60:27-31.