Available online on www.ijddt.com
International Journal of Drug Delivery Technology 2018; 8(4); 159-165
doi: 10.25258/ijddt.8.4.2

ISSN: 0975 4415

Research Article

Formulation and Evaluation of Patient Centric Paper Dosage Form of Donepezil Hydrochloride

Arun Radhakrishnan, Gowthamarajan Kuppusamy*, Soni Abishek

Department of Pharmaceutics, JSS College of Pharmacy, Udhagamandalam, JSS Academy of Higher Education and Research, Mysuru, India

Received: 25th May, 18; Revised: 25th Oct, 18, Accepted: 8th Nov, 18; Available Online: 25th Dec, 2018

ABSTRACT

The aim of this study was to develop a dose flexible paper dosage containing donepezil hydrochloride, with fast disintegration time and suitable mechanical strength, for the treatment of Alzheimer's disease. Hydroxypropylmethylcellulose and pectin served as the hydrophilic polymeric bases of the ODF. The uniformity, in vitro disintegration time, drug release and the folding endurance of the ODF were examined. The in vitro results showed that 90% of donepezil hydrochloride was released within 20 minutes with mean disintegration time of 32 seconds. The result of the film flexibility test showed that the number of folding time to crack the film was average 200 times, an indication of sufficient mechanical property for patient use. All the required evaluations were recorded. ODF containing 30 mg of sucralose were more superior to saccharin and aspartame in terms of taste, aftertaste, mouthfeel, and acceptance. Furthermore, the film forming capacity of the polymers was evaluated and resulted better than single polymers. The drug and polymers showed no major interactions which were displayed by the DSC studies. As per the required results for paper dosage form, all parameters were showing satisfactory results. Formulation F3 was selected as the ideal formulation for the development of paper dosage form. F3 showed a disintegration time less than 35 sec, which shows that the drug will start releasing in less than a minute and more than 60% drug was released in 5 mins which were required for the quick onset of action.

Keywords: Paper dosage form, Fast dissolving films, Dose flexibility, Patient-centric, Patient-friendly.

INTRODUCTION

Alzheimer disease is one of the most common causes of dementia, which results in 60% of cases of late-life cognitive dysfunction. For the treatment of mild to moderate Alzheimer disease, donepezil is prescribed. Donepezil hydrochloride shows its action by reversibly inhibiting the enzyme acetylcholinesterase, which increases the concentration of acetylcholine through reversible inhibiting its hydrolysis by acetylcholinesterase[1].

During the past few decades, orally disintegrating films (ODFs) have developed improved acceptance and patient compliance[9]. ODFs, which are commonly prepared by using hydrophilic polymers and disintegrants which rapidly disintegrates/dissolves when placed on the tongue, as they immediately disintegrate and dissolves upon being exposed to saliva, resulting in the release of drug from the dosage form[4]. Orally disintegrating tablets have a disadvantage of the risk of friability and fear of choking, although ODFs covers that flaw as well as increasing the patient compliance. Currently, ODFs are accessible for allergy, hypertension, acidity, pain, etc[7]. ODFs can be administered without using water for the absorption of the drug which offers ease in drug administration[8]. Orally disintegrating or dissolving films offer a potential solution for a successful pediatric drug administration. The ease of drug administration and reduced choking risks combined with fast disintegration in the mouth prove that these dosage forms can be used as the choice of drug administration, especially for pediatric use[2]. Oral films have a lot of advantages as compared to conventional drug delivery systems in terms of characteristics like availability of a larger surface area for faster soaking with saliva, disintegration, and dissolution. ODFs also have some clinical advantages, such as dosing accuracy and flexibility[10]. This dosage form is pediatric and geriatric patient-friendly and has an ease of portability and handling. The disadvantages associated with these films are the smaller drug load given due to their smaller size and thickness[3]. These films are sensitive to humidity and temperature so they require special packaging[5].

Patient-Centric Dosage Form

A Patient-Centric approach is a way healthcare systems can establish alignment with patient's wants, needs,and preference. Many geriatric patients find it difficult to swallow solid dosage forms such as tablets and capsules, therefore, ease ofadministration of dosage form is of paramount importance. As a result, Personalised medicine and customized drug delivery systems are the patient-centric approaches to increase patient compliance. Personalised medicine, also termed as precision medicine is a medical procedure that separates patients into a

Author for Correspondence: gowthamsang@jssuni.edu.in

Table 1: Formulation batches for paper dosage form.

Ingredients	F1	F2	F3	F4	F5
HPMC E15	200	400	600	800	1000
Pectin	200	400	600	800	1000
Glycerol	3	3	3	3	3
CMC	20	20	20	20	20
Sodium starch glycolate	20	20	20	20	20
Sucralose	30	30	30	30	30
Water	q.s	q.s	q.s	q.s	q.s

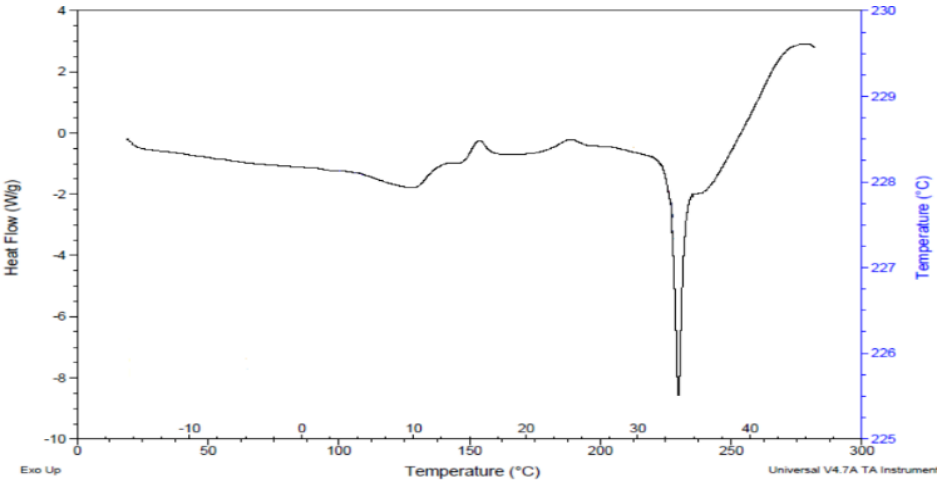

Figure 1:DSC Thermogram of Donepezil hydrochloride.

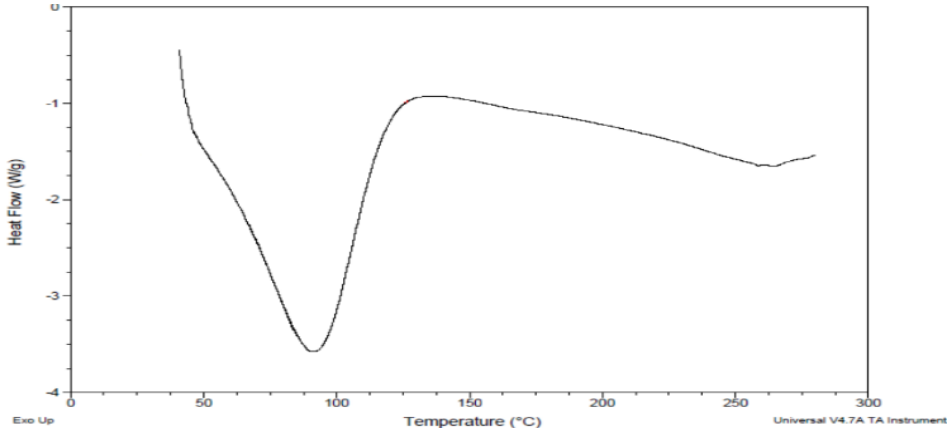

Figure 2: DSC Thermogram of HPMC E15.

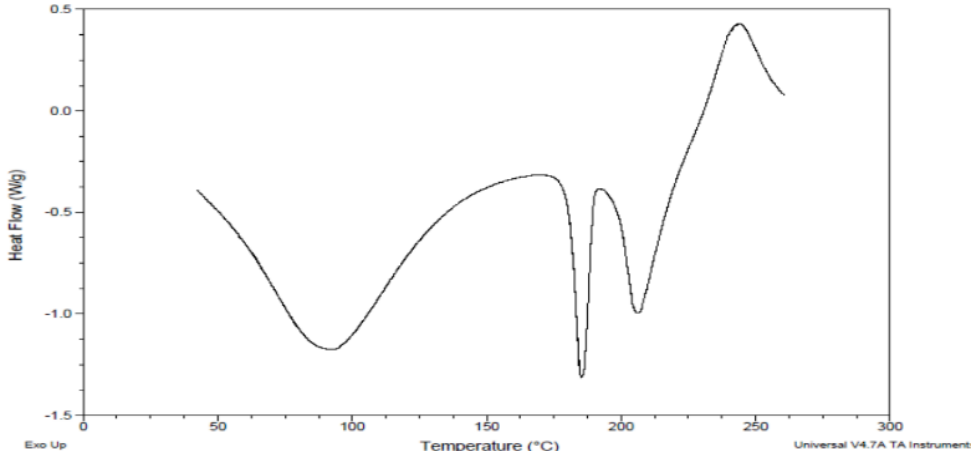

Figure 3: DSC Thermogram of Pectin.

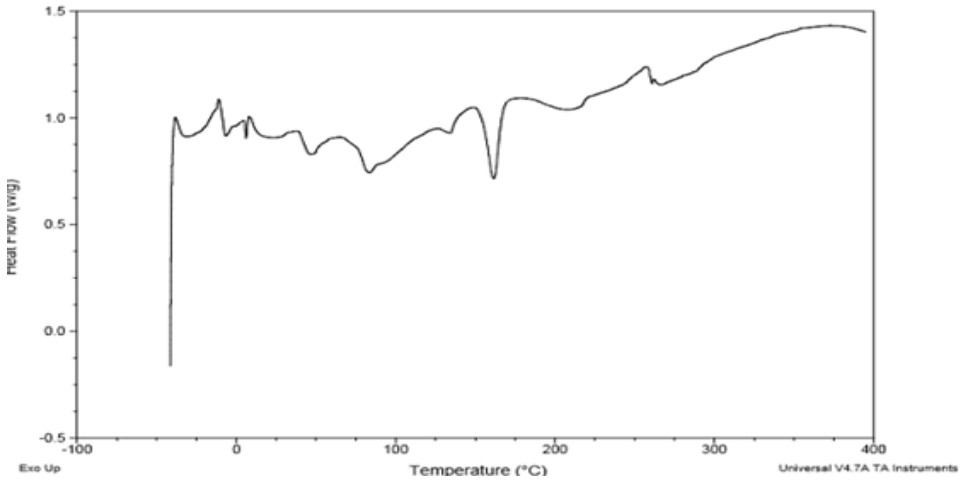

Figure 4: DSC Thermogram of the physical mixture of drug and polymers.

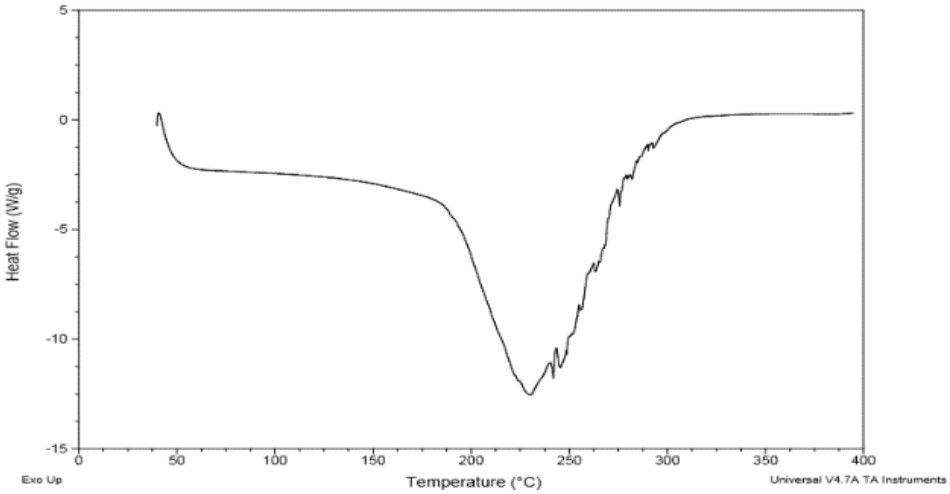

Figure 5: DSC Thermogram of the ideal formulation batch.

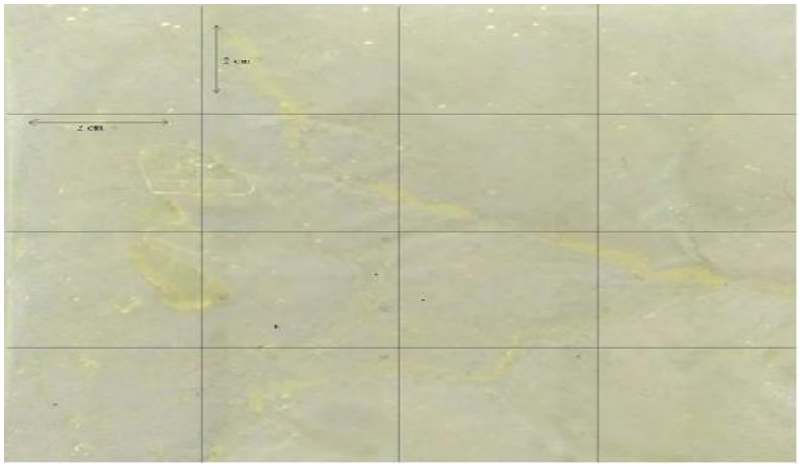

Figure 6: Dose flexible Paper Dosage Form.

different group or as an individual patient based on their symptoms or predicted response. Dose flexibility is the major challenge that physicians face while prescribing the drug, Fast dissolving films can be customized in order to create a patient-friendly, patient-centric dosage form with dose flexibility which can improve the dose precision. Thus, theresulting customized fast dissolving film is termed as a paper dosage form.Paper dosage form offers dose flexibility and easy administration thus developing as a patient-friendly dosage form and especially in case of pediatrics.The paper dosage form is developed by customizing the fast dissolving film and incorporating dose flexibility. Therefore, in this work, we are focussed on developing a patient-friendly dose flexible paper dosage form, which targets the patient-centric approach as a customized drug delivery system.

MATERIALS AND METHODS

Table 2: The Results of Weight, Thickness, Surface pH and Folding Endurance.

Formulation Code	Weight (mg)	Thickness (mm)	Surface pH	Folding endurance
F1	43.66 ± 0.942	0.20 ± 0.020	6.74	184
F2	45.40 ± 1.014	0.27 ± 0.153	6.81	197
F3	48.15 ± 1.321	0.30 ± 0.008	6.71	201
F4	53.06 ± 1.194	0.33 ± 0.009	6.62	187
F5	58.51 ± 1.291	0.37 ± 0.026	6.93	212

Materials

Donepezil hydrochloride was a gift from Dr. Reddy's Laboratories, Hyderabad. HPMC E15 was purchased from The Dow Chemical Company. Pectin, Carboxymethyl cellulose,and Glycerolwere purchased from SD fine chemicals, Mumbai. Sodium Starch Glycolate was purchased from Loba Chemie, Mumbai.

Methods

Differential Scanning Calorimetry (DSC)

Differential scanning calorimeter calibrated with indium was used to perform DSC. The samples of Donepezil hydrochloride, HPMC E15, Pectin, Physical mixture and the drug-loaded film were heated at a heating rate of 10°C/min from 5 to 300°C in an inert nitrogen atmosphere. The DSC thermograms of the above samples were traced[11].

Formulation of Patient-Centric Paper Dosage Form

Solvent Casting Method

The solvent-casting method was used to prepare the Fast Dissolving Film. The ingredients which were soluble in water were dissolved to form a clear, semi-liquid solution. The API and the excipients like sweetener, plasticizer etc. were dissolved as a mixture in a very small amount of the suitable solvent. This mixture was added to the semi-liquid solution and stirred to form a clear homogeneous solution. The solution was kept aside for 12 hrs for De-aeration. The removal of air bubbles is important in order to obtain a uniform film with uniform thickness. The resulting solution was cast on a Petri dish as a film. The film was allowed to dry at a temperature of 45º for 24 h. The dried film was peeled off and cut into pieces of the desired size[12,17].

Calculation of dose

The dose of donepezil hydrochloride is 5mg. Therefore the amount of donepezil hydrochloride in a film of diameter 2cm is 5mg.

Area of the petri dish of 9.7cm diameter is 74cm^2

Amount of the drug to be present in the 4cm^{2}film is 5mg.

Amount of drug present to be added to the 74cm^2 area of the petri dish is 185mg.

The amount of donepezil hydrochloride required for petri dish of area 74cm^2 is 185 mg so that each film of 4cm^2 area contains 5mg of donepezil hydrochloride.

Evaluation parameters

Weight of Films

To make certain that the drug and the additives are present in an equal amount in the formulation, the films are weighed on the analytical balance and the average weight of the films is determined. The films are required to have a constant weight[13].

Thickness of the film

The thickness of the film should be uniform to confirm uniform distribution of the drug. A screw gauge which is used to measure the thickness of a dosage form was placed at different positions of the film and the thickness was measured. The average thickness was thus calculated[14].

Surface pH

To determine the pH value of the film, it was dissolved in 10 ml distilled water and the pH of the solution was measured using pH meter. Appropriate and uniform pH value confirms the fast dissolution of the film in the mouth[15].

Folding endurance

The folding endurance is measured to indicate the brittleness of the film. Folding endurance is expressed as the number of folds at which the specimen starts breaking or starts developing visible cracks. A small strip of 4 cm2 was used for the test. The strip was folded at the same plane several times. The process was repeated until visible cracks were observed on the film surface[13].

Wetting time

Wetting time is measured to observe the disintegration time of dosage form. The lower the wetting time of the film, the faster is its disintegration. Wetting time is related to the contact angle of the dosage form. To measure the wetting time, the oral film was placed on tissue paper folded twice. The tissue along with the film was placed in a Petri dish containing 6 ml of water. The time taken for the wetting of the entire film is noted.

Water absorption rate

Water absorption rate was measured by using a piece of tissue paper folded twice, placed in a Petri dish containing 6 ml of water. A film was weighed and placed on the piece of tissue. After the film was totally wet, the weight of the wet film was measured and Water absorption ratio (R) was calculated using the following equation:

$R=100(Wa/Wb)$

Where,

Wb -Weight of tablet before the absorption of water.

Wa -Weight of tablet water the absorption of water.

Disintegration test

The disintegration time of ODF's can be expressed as the time in seconds taken by the film to break down when it comes in contact with saliva or water. To measure the disintegration time, the film was dipped in 10ml of water in a beaker manually. The beaker was gently shaken and the time taken by the film for dissolving completely in the water was noted. The time taken for the film to disintegrate should be 30 seconds or less. The disintegration time described for ODT's under CDER guidance can be applied for ODF's as no special guidance is mentioned for quality control test for fast dissolving films[18].

Drug content

The drug content was measured by dissolving a certain area of the film (2cm×2cm) in 100 ml water in a volumetric

Table 3: The Results of Wetting Time, Water Absorption Test, Disintegration Time and Drug Content.

Formulation Code	Wetting time (sec)	Water absorption test (%)	Disintegration time (sec)	Drug content (%)
F1	51	72.5	28 ± 0.942	96.77 ± 1.745
F2	58	74.9	33 ± 1.247	97.12 ± 0.460
F3	54	78.3	32 ± 1.242	98.07 ± 0.204
F4	62	75.9	36 ± 1.356	97.33 ± 0.825
F5	65	74.4	39 ± 1.226	97.57 ± 0.276

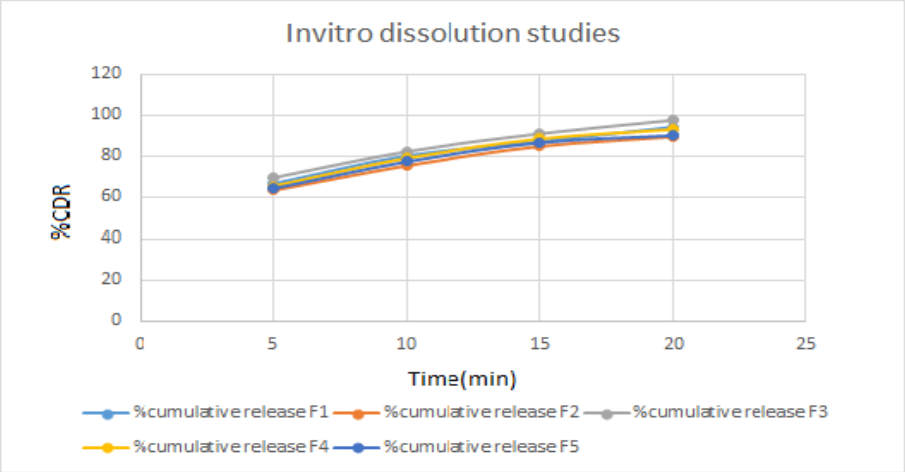

Figure 7: Graph showing invitro drug dissolution studies.

flask. The flask was shaken for 10 min and the resulting solution was filtered using Whatman filter paper to filter out the insoluble excipients. From the filtered solution, 1ml of the solution was diluted up to 10ml with water and the absorbance was measured using UV spectrophotometer at 271nm and the drug content was calculated[18,19].

In vitro- Dissolution test

USP paddle method was used for the in vitro drug dissolution study. The dissolution was carried out in 900 mL of 6.8 phosphate buffer as a dissolution medium at a temperature of 37.0±0.5°C. The rotation speed was maintained at 50 rpm. At the time intervals of 5, 10, 20 and 30 min, 3 mL of aliquots were withdrawn and replaced with an equal volume of pre-warmed dissolution medium immediately. The withdrawn samples were assayed to measure the amount of drug release using UV spectrophotometer at an absorbance of 244nm[16].

RESULTS AND DISCUSSIONS

Differential scanning calorimetry

Differential Scanning Calorimeter (DSC) allows the fast evaluation of possible incompatibilities because it shows changes in the appearance, Shift of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction.

Donepezil hydrochloride showed a sharp endothermic peak at 229.85ºC (Fig. 1), corresponding to its melting point. Similarly, HPMC E15 and Pectin showed the endothermic peaks at 91.57ºC and 92.61ºC respectively. There is a slight shifting of melting endotherm of Donepezil hydrochloride in the physical mixture as shown in Fig. 4 indicated that there is no interaction between drug and the excipients. The ideal formulation batch showed 231.30ºC which shows no interaction between drug and excipients in the formulation form and the endothermic peak is corresponding to the endothermic peak of the drug showing the uniformity of drug in the dosage form.

Formulation of the paper dosage form

Usage of dose flexible paper dosage form

Oral soluble films come in different dimensions according to the dose requirement. Paper dosage form comes in the dimension, i.e. 4cm^2 (2cm × 2cm) contains 5mg of the drug and if the patient requires half the single dose then paper dosage form can be torn into half to fulfill that requirement i.e. 2cm^2 (1cm × 1cm). This work provides a dose flexible paper dosage form which brings in the 'tear and use' concept. The paper dosage form will be prepared with the markings of a single dose (Fig.6) which will be easier to use and administer, the patient can just tear the required dose and administer. There will be no need of multiple packaging and store as the film will be a single film, thin as paper increasing the patient compliance by reducing the need of taking multiple dosage form sheets for taking the medication. The single sheet of the paper dosage form can be given for the whole treatment process of the patient.

Evaluation parameters

Weight of films

All the formulation have acceptable weights for the formulation of this work. Less weight shows a better disintegration time. Table 2 displays the weights obtained from all formulations. The results display that increase in the polymer concentration increases the weight of the formulation.

Thickness

All the films have a uniform thickness throughout. The average thickness of all the formulations ranged between

0.20 to 0.40 mm. The disintegration time is directly related to the thickness of the films and the observed results were satisfactory for paper dosage form. The results show that increase in the concentration of polymers increases the thickness of the film as well as the disintegration time. Table 2 displays the results obtained.

Surface pH

The surface pH was found to be in the range of 6.60 to 6.95 which is close to salivary pH, which indicates that films may have less potential to irritate the oral mucosa, thereby they are comfortable. All formulation shows good surface pH value. Table 2 displays the surface pH of all formulations.

Folding endurance

Folding endurance tests have been used to estimate the ability of oral film prepared to withstand repeated bending, folding, and creasing without breaking. Folding endurance has also been used for measuring the deterioration of film upon aging. The results shown in table 2 suggest that all the formulations have a flexible and durable strength required to avoid the film defects.

Wetting time

This test is an important criterion to determine the ability of the disintegrant to swell and release the drug particles into the water. The results tabulated shows that all formulation got wetted within the range of 50-65 sec. Satisfactory results were obtained in order to get a better disintegration of the film shown in table 3.

Water absorption test

All the formulations show good water absorption property. Water absorption test shows the wetting capacity of different concentrations of polymers. All results are acceptable for the formulation of this work. Table 3 displays the results of water absorption test.

Disintegration time

Disintegration time suggests the time taken for the formulation to disintegrate in the salivary pH. All the formulation shows acceptable results for paper dosage form evaluation. Table 3 displays the disintegration time of different formulations. All formulation showed satisfactory disintegrating time. The results suggest that increase in the polymer concentration also increases the disintegration time.

Drug content

The drug content of all the films was in the range of 95.54 to 98.68 suggesting that drug was uniformly dispersed throughout all films. Formulation F3 showed the highest drug content which is given in table 3.

In-vitro dissolution studies

From the in-vitro release studies, we came to the conclusion that the concentration of the polymers directly affects the drug release. Satisfactory results were obtained from the formulations. F3 formulation shows the best drug release from the dosage form. Fig. 7 displays the obtained results of all formulations. All the formulation batches showed more than 90% drug release within 20 mins.

CONCLUSION

With help of literature all the components required for formulation of paper dosage form were taken and optimization of different concentrations of a combination of polymers viz. HPMC E15 and pectin were carried out. All formulation batches gave good results in accordance with the study, Formulation F3 was selected as the ideal formulation as it showed better results than the other formulation batches. All the evaluation parameters were performed and the ideal batch showed an average of 32 mins disintegration time with 97% of drug release in about 29 mins. Satisfactory results were obtained from this work to comply with the objectives of the formulation. This work was satisfactory in order to formulate a customized drug delivery system to increase patient compliance.

REFERENCE

1. Liew KB, Tan YT, Peh KK. Characterization of oral disintegrating film containing donepezil for Alzheimer disease. AAPS PharmSciTech 2012; 13:134-142.
2. Irfan M, Rabel S, Bukhtar Q et al. Orally disintegrating films: A modern expansion in drug delivery system. Saudi Pharm J 2016; 24: 537–546.
3. Karki S, Kim H, Na SJ et al. Thin films as an emerging platform for drug delivery. Asian J. Pharm 2016; 11: 559–574.
4. Shanmugam S. Oral Films: A Look-Back. ClinPharmacolBiopharm 2016; 5: 124.
5. Irfan M, Rabel S, Bukhtar Q, Qadir MI, Jabeen F, Khan A. Orally disintegrating films: a modern expansion in drug delivery system. Saudi Pharm J 2016; 24:537-546.
6. Dixit RP, Puthli SP. Oral strip technology: overview and future potential. J controlled release 2009; 139:94-107.
7. Thakur N, Bansal M, Sharma N, Yadav G, Khare P. Overview "A novel approach of fast dissolving films and their patients". AdvBiol Res 2013; 7:50-58.
8. Kumar R, Rai AK, Verma NK, Vishwakarma DK. Fast dissolving drug delivery system: Innovative strategies for drug application. Int J Pharm Drug Anal 2017; 5:219-228.
9. Liew KB, Tan YT, Peh KK. Effect of polymer, plasticizer,and filler on orally disintegrating film. Drug Dev Ind Pharm 2014; 40:110-119.
10. Patel NA, Shah DP, Patel TJ. A novel approach for buccal drug delivery system-buccal film. Pharma Sci Monit 2016; 7:166-183.
11. Patil P, Shrivastava SK. Formulation, evaluation,and optimization of fast dissolving oral film of selective antihypertensive drug. World J Pharm PharmSci 2014; 3:996-1060.
12. Khatoon N, Rao NR, Reddy BM. Formulation and evaluation of oral fast dissolving films of montelukast sodium. Int J Pharm Sci Res 2014; 5:1780- 1787.
13. Nair SS, Padmanabhan R, Sreena K. Development and Evaluation of Fast Dissolving Oral Thin Film Containing Prochlorperazine Maleate. Eur J Pharm Med Res 2016; 3:379-384.
14. Kadam VS, Bharkad VB, Shete GA, Jameel A, Shendarkar GR, Jadhav SV. Formulation and evaluation of fast dissolving oral film of

metoclopramide HCL. World J Pharm PharmSci 2017; 6:2052-2066.
15. Buddhadev S, Buddhadev S. Formulation and evaluation of fast dissolving film of etophylline. Int J Appl Pharm Biol Res 2017; 2:48-55.
16. Harini C, Sowjanya CH, Kumar KS. Formulation and evaluation of mouth dissolving film containing cetirizine hydrochloride. Int J Adv Res Med Pharm Sci 2016; 1:20-25.
17. Patil PS, Patil SG, Tadavi SA, Gujarati NA, Pawar SP. Formulation and evaluation of fast mouth dissolving film of metoprolol succinate. World J Pharm PharmSci2017; 6:657-669.
18. Deepthi A, Reddy BV, Navaneetha K. Formulation and evaluation of fast dissolving oral films of zolmitriptan. Am J Adv Drug Delivery 2014; 2:153-163.
19. Upreti KA, Kumar L, Anand SP, Chawla V. Formulation and evaluation of mouth dissolving films of paracetamol. Int J Pharm Pharm Sci 2014; 6:200-202.