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Research Article

FORMULATION OF FAST DRUG DELIVERY SYSTEM

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Abstract

Recently fast dissolving dosage forms (FDDF) have started gaining popularity and acceptance as new drug delivery systems due to their unique properties. They quickly disintegrate and dissolve in the mouth and can be administered without water, making them particularly suitable for paediatric and geriatric patients. FDDF include tablets, films and microspheres. Tablets are the most commonly used amongst them.

The aim of the present investigation was to develop and formulate fast dissolving dosage forms of the film type.

1. Introduction

Orally disintegrating drug delivery systems were originally devised by scientists at Wyeth Laboratories in the UK during the 1970s and their research lead to the outcome of Zydis, a patented formulation technology. FDDF are referred by different names like fast dissolving, porous tablet, melt-in-mouth, oro-dispersible, quick dissolving, orally disintegrating or rapidly disintegrating dosage forms (1,3,4). The commonly available patented formulations are freeze dried type of dosage forms, which possess better convenience for use, enhanced bioavailability, and higher stability of the dosage form

Fast dissolving or quick dissolving dosage forms have acquired great importance in the pharmaceutical industry due to their unique properties and advantages (1, 2). They undergo disintegration in the salivary fluids of the oral cavity of the patient within a minute, where they release the active pharmaceutical ingredient. The major amount of the active pharmaceutical ingredient is swallowed orally with the saliva where subsequent absorption takes place in the gastro-intestinal tract (3, 4). The rapidly dissolving dosage forms were introduced in 1970's as an alternative to the conventional tablet and capsule which require swallowing of the dosage form (3-5).

The lyophilized wafers, thin strips and films are newer types of rapidly dissolving dosage forms. These dosage forms can be manufactured using a variety of technologies, including freeze drying, vacuum drying, spray drying by using super disintegrants and molding methods (1, 2).

Fast dissolving tablets are available in the market for a variety of drugs however; fast dissolving films (FDF) were initially introduced in the market as breath fresheners and personal care products such as dental care strips and soap strips. However this dosage form has now also been introduced in the United States and European pharmaceutical markets for therapeutic benefits (2,5-8). A film or strip comprises of water soluble and/or water swellable film forming polymer due to which the film or strip dissolves instantaneously when placed on the tongue in the oral cavity. The first of this kind of oral strips were developed by the major pharmaceutical company Pfizer who named it as Listerine® pocket packs™ and were used for mouth freshening. Chloraseptic® relief strips were the first therapeutic oral thin films which contained benzocaine and were used for the treatment of sore throat (8).

The FDF are essentially prepared using water soluble and fast disintegrating polymers which also possess good film forming properties like hydroxypropyl methylcellulose (HPMC), pullulan, polyethylene oxide (PEO), polyvinyl pyrolidone (PVP) and hydroxypropylcellulose (HPC) (5,9). Although HPMC is more commonly used for FDF formation, pullulan is also often used as a film former due to its excellent film forming property. Pullulan is a natural polysaccharide produced from starch by cultivating black yeast Aureobasidium pullulans. It is a white, tasteless, odourless water soluble powder. Pullulan PI-20 grade is the deionised form of pullulan having an average molecular weight of 2,00,000 daltons (10). FDF using pullulan can be manufactured using solvent casting, hot melt extrusion or compression moulding. Solvent casting is the most common and traditional method (2).

Cetirizine hydrochloride (CTZ) is an orally active and selective H1-receptor antagonist used in seasonal allergic rhinitis, perennial allergic rhinitis and chronic urticaria. CTZ is a white, crystalline water soluble drug possessing bitter taste properties (11,12). Due to sore throat conditions, the patient experiences difficulty in swallowing a tablet type of dosage form. Thus, a FDF would serve as an ideal dosage form for the patients as well as paediatric patients who find it difficult to swallow the tablet. Due to its ease of usage and high acceptability, FDF of CTZ were formulated in the present investigation. Combination of sweeteners, flavours and acidifying agents were used for taste masking in the optimized batch. The FDF are characterized for mechanical properties like thickness, tensile strength,

elasticity, elastic modulus, environmental scanning electron microscopy, in-vitro and in-vivo disintegration time and in-vitro dissolution studies (13,14).

2. Materials and Equipments

Materials Used

Materials	**Name of Company**
Cetirizine hydrochloride	Gifted by Troikaa Pharmaceuticals Ltd,
Pullulan	Gifted by Hayashibara Company Ltd,
Sucralose	Gifted by Alkem Lab Ltd, Ankleshwar,
Citric acid anhydrous	Central Drug House (P) Ltd, New Delhi
Menthol	S.D. Fine Chem Ltd, Mumbai
Polyethylene glycol 400	S.D. Fine Chem Ltd, Mumbai
Aspartame	Hi-media Lab Pvt Ltd, Mumbai
Passion fruit and lemon flavours	Pentagon trading company, Ahmedabad

All other chemicals used were of analytical grade and were used without further purification. Double distilled water was used for the study.

Equipments used

Equipments	**Name of Company**
Hot air oven	EIE Instruments, Ahmedabad, India
Universal testing machine	Lloyd, UK model LR 100 K, UK
Fourier transfer infra-red	Jasco FTIR model 6100, Japan
USP dissolution apparatus XXIV	Electrolab, Mumbai, India
Environment scanning electron microscope	Philips, XL 30 model, Netherlands

3. Films and Method of Preparation of Rapidly Dissolving its Evaluation

Preparation of rapidly dissolving films (FDF)

The FDF of cetirizine hydrochloride using pullulan were prepared by solvent casting method (2). An aqueous solution of the polymer pullulan was prepared in distilled water. Cetirizine hydrochloride was added to the aqueous polymeric solution. This was followed by addition of menthol which was previously dissolved in ethyl alcohol (95%) and plasticizers like PEG 400 or glycerol. Sweeteners like aspartame and sucralose were also added to the above solution. Citric acid and flavour were also mixed with it. The solution was casted on a petridish (diameter 9 cm) and dried at room temperature for 24 hr. The film was carefully removed from the petridish, checked for any imperfections and cut into the required size to deliver the equivalent dose (2 x 2 cm^2) per strip. The samples were stored in a dessicator at relative humidity 30-35 % until further analysis. Film samples with air bubbles, cuts or imperfections were excluded from the study.

Evaluation

The FDF were evaluated for the following parameters-

1. Fourier transfer infra red spectroscopy (FTIR)
2. Measurement of mechanical properties of the FDF (16,17)
3. In-vitro disintegration studies (2,13,14)
4. In-vivo disintegration studies (14)
5. In-vitro dissolution studies (14,15)
6. Environment Scanning electron microscopy (ESEM) (18,19)
7. Taste evaluation (20)

4. Results and Discussion

Pre-formulation study

Pre-formulation study for the drug and excipients was conducted. No drug-excipient or excipient-excipient interaction was observed.

Calculation was performed for film casting according to the total area of the sheet. Total area for a single film was 4

cm^2. Total area of the sheet was 100 cm^2. Total number of strips made from one sheet was 25. One strip was prepared so as to contain one dose equivalent to 10 mg cetirizine hydrochloride.Thus, a sheet of 25 strips will contain 250 mg cetirizine hydrochloride.

Various casting surfaces were used for proper separation property of the film from petridish namely plastic, glass, formica and Teflon.

Initial trials as shown in Table 1 were taken to check the film formation property.

Preliminary trials

Table-1: Preliminary trials using pullulan for film formation.

Ingredients (mg)/	P1	P2
Pullulan	200	500
Distilled water (ml)	10	10
Type of casting surface		
Glass	No	No
Plastic	No	No
Formica	Partial	Partial
Teflon	Yes, thin brittle film	Yes

*Batch size 25 strips

The films casted on glass and plastic petridishes could not be separated. When formica sheet was used uniform and complete film separation could not be obtained. The film using 200 mg pullulan were very thin and unacceptable. Thus, further trials were taken using 500 mg pullulan as film forming polymer using Teflon sheet.

Table-2: Formulation trials using Teflon as a casting surface.

Ingredients (mg)/ Batch*	P3	P4
Pullulan	500	500
CTZ	250	250
Menthol	10	15
Distilled water (ml)	10	10
Film separation	Yes, brittle film	Yes, brittle film

*Batch size 25 strips

As observed in Table 2, complete removal of the film was not possible due to brittle nature of the film. Therefore, addition of plasticizer was found to be necessary and was tried in further formulation trials.

Experimental trials

Table-3: Effect of addition of plasticizer for efficient film separation.

Ingredients (mg)/ Batch*	P5	P6
Pullulan	500	500
CTZ	250	250
Menthol	15	15
PEG 400	150(0.2:1)	300(0.4:1)
Distilled water (ml)	10	10
In-vitro disintegration time	17.5	17.5
Taste masking	+	+

*Batch size 25 strips

Good film separation was obtained using plasticizer PEG 400 on teflon surface. The in- vitro disintegration time for batches P5 and P6 was 17.5 sec which was acceptable. The films had unacceptable taste. Thus, addition of menthol and aspartame was tried to improve the taste.

Table-4: Effect of addition of menthol and aspartame for taste masking.

Ingredients (mg)/ Batch*	P7	P8
Pullulan	500	500
CTZ	250	250
Menthol	37.5	37.5
Aspartame	75	75
PEG 400	150	300
Distilled water (ml)	10	10
In-vitro disintegration time	20	20
Taste masking	+	+

*Batch size 25 strips

The in-vitro disintegration time of batches P7 and P8 was 20 sec. However, addition of menthol and aspartame (Table 4) could not produce taste masking effect. Further trials were taken using combination of sweeteners i.e. aspartame and sucralose along with acidifying agents like citric acid. Aspartame in presence of menthol could not produce taste masking (batches P7 and P8) which might be due to moderate sweetening effect of aspartame. Therefore, menthol was not used in further trials and a combination of moderate and intense sweeteners was tried i.e. aspartame and sucralose.

Table-5: Formulation trials using combination of sweeteners and citric acid for taste masking.

Ingredients (mg)/ Batch*	PT1	PT2	PT3	PT4	PT5
Pullulan	500	500	500	500	500
CTZ	180	180	180	180	180
Aspartame	75	112	112	112	112
Sucralose	90	90	90	90	100
PEG 400	338	353	381	409	396
Distilled water (ml)	10	10	10	10	10
Flavour (ml)	-	-	0.1	0.1	0.1
Citric acid	-	-	70	140	100
In-vitro disintegration time (sec)	25	30	35	35	35
Taste masking	++	++	+++	++	++

Table-6: Comparative in-vitro dissolution study of batch PT1, PT3 and PT5 in distilled water.

Time (sec)	Cumulative % drug release		
	PT1	PT3	PT5
2	100	100	100

Table 6 shows in-vitro dissolution study for batches PT1, PT3 and PT5. The result indicates complete drug release in 2 min for all 3 batches. This indicates inherent nature of pullulan containing films where the in-vitro dissolution is fast and not affected by addition of other excipients. As none of the batches had acceptable taste further trials were taken after addition of flavours and citric acid.

Table-7: Initial trials for optimization of taste masking by addition of flavours and citric acid.

Ingredients (mg)/ Batch*	PA1	PA2	PA3	PA4
Pullulan	500	500	500	500
CTZ	180	180	180	180
Aspartame	112	112	112	112
Sucralose	100	100	100	100
* Batch size 18 strip	356	356	356	356
Flavour (ml)	-	0.1	0.1	0.15
Citric acid	-	-	70	100
Distilled water (ml)	10	10	10	10
In-vitro disintegration time (sec)	35	35	35	35
Taste masking	++	++	++	++

* Batch size of 18 strips

Taste masking of the film could not be achieved using passion fruit flavour and acidifying agents like citric acid. Increased quantity of passion fruit flavour did not result in taste masking. Further trials were taken using other flavours like lemon and orange along with increased amount of citric acid. All batches PA1 to PA4 had in-vitro disintegration time of 35 sec.

Table -8: Optimization trials for taste masking using different types of flavours.

Ingredients (mg)/ Batch*	PA5	PA6	PA7
Pullulan	500	500	500
CTZ	180	180	180
Aspartame	112	112	112
Sucralose	100	100	120
PEG 400	356	356	356
Distilled water (ml)	10	10	10
Flavour (ml)	0.15	0.15	0.15
Citric acid	100	100	120
In-vitro disintegration time	25	25	30
In-vivo disintegration time	20	20	20
Taste masking	+++	+++	++++

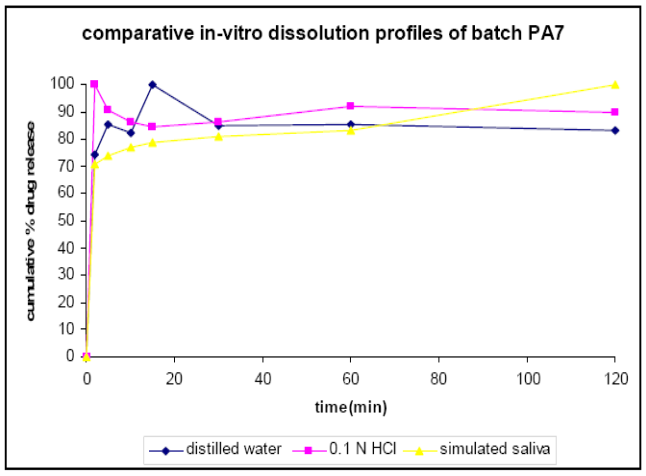
* Batch size of 18 strips, CTZ refers to Cetirizine hydrochloride

Batch PA5 could not produce acceptable taste masking in presence of lemon flavour and citric acid (5.56 mg/strip). PA6 containing orange flavour and citric acid (5.56 mg/strip) was too unacceptable in taste. Optimized taste masking could be achieved in batch PA7 with lemon flavour and slightly higher amount of citric acid and was evaluated for other parameters. Optimized taste masked batch PA7 contained lemon flavour and citric acid (6.67 mg/strip) in addition to sweeteners, aspartame and sucralose. It could be concluded that selection of flavour plays critical role in taste masking of CTZ containing FDF.

Table-9: In-vitro dissolution study of optimized batch PA7 in different dissolution medium.

Time (min)	Cumulative % drug release		
	Dissolution medium		
	Distilled water	0.1N HCl	Simulated saliva
2	74.46	100	70.93
5	85.51	-	73.76
10	82.23	-	77
15	100	-	78.65
30	-	-	80.78
60	-	-	83.4
120	-	-	100

Figure 1: Comparative in-vitro dissolution profile of batch PA7



The in-vitro dissolution study of the optimized batch indicated the 75% drug released in distilled water, 100% in 0.1N HCl and 71% in simulated saliva in 2 minutes. The total drug release was observed in 15 min, 2min and 2 h in simulated saliva.

Environment scanning electron microscopy (ESEM)

The ESEM of pullulan in Figure 2a indicated irregular shaped particles at 65x magnification. Cetirizine hydrochloride particles could not be seen distinct as such. On dispersing it in acetone distinct cylindrical particles could be observed at 350x magnification as shown in Figure 2b. The optimized film shown in Figure 2c at 350x magnification showed uniform film with few pores and cetirizine particles without any striations could be seen.

Figure 2a: ESEM of pullulan powder at 65x magnification.

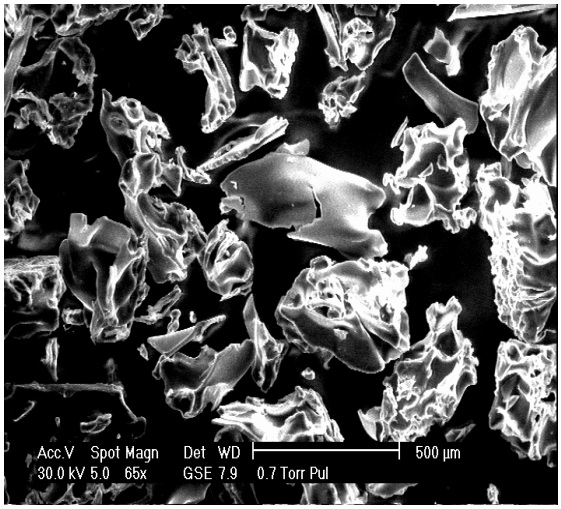


Figure 2b: ESEM of Cetirizine hydrochloride at 350x magnification.

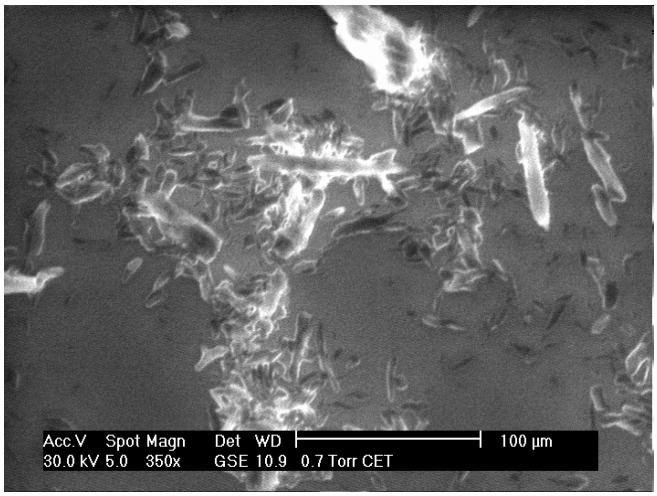
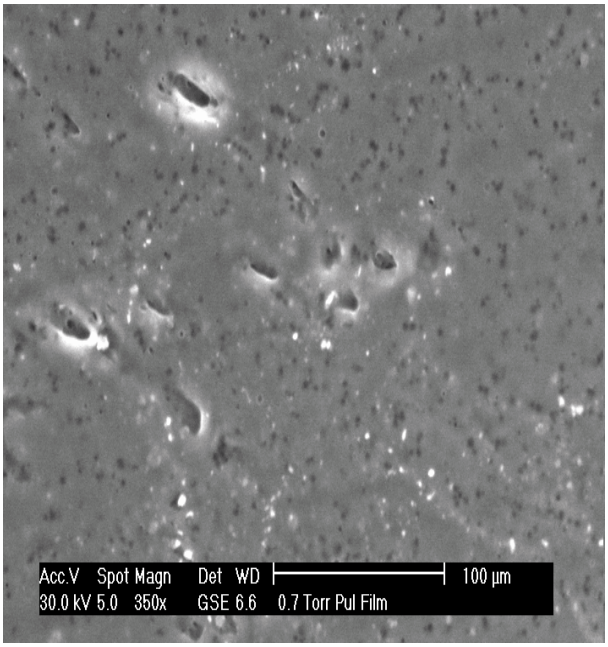


Figure 2c: ESEM of batch PA7 film at 350x magnification.



Conclusion

FDF of CTZ was manufactured using pullulan as a film forming agent. Type of casting surface played an important role in the film separation. PEG 400 was found to be suitable as a plasticizer. Addition of sweeteners aspartame, sucralose, citric acid and lemon flavour produced optimized taste masking in batch PA7. It could be concluded that type of flavour played a critical role in taste masking. The optimized film was uniform with few pores without any striations as indicated in ESEM. CTZ particles were uniformly distributed throughout the film. The results of study of mechanical properties indicated batch containing the polymer alone exhibited highest tensile strength. In presence of plasticizer the tensile strength decreased from 23.7 to 9.7 N/mm^2. The optimized batch had acceptable tensile strength 12.5 N/mm^2. The % elongation of all the batches was very less (1.5-3.5). It increased upon addition of plasticizer which was in agreement with role of plasticizer. The elastic modulus value indicated toughness of the film. The elastic modulus values were high for the film containing polymer alone. Addition of excipients reduced toughness of the film. Excellent film properties were obtained using pullulan along with rapid disintegration.

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