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FORMULATION AND EVALUATION OF CETRIZINE DIHYDROCHLORIDE FAST DISSOLVING FILM FOR PEDIATRICS

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ABSTRACT

This study aimed to develop films for potential delivery of Cetrizine Dihydrochloride via the buccal mucosa of paediatric patients. Films were prepared using hydroxy propyl methyl cellulose (HPMC E-15), hydroxy propyl methyl cellulose (HPMC K-15), hydroxy propyl methyl cellulose (HPMC K-100), hydroxyl propyl methyl cellulose (HPMC K-100), polyvinyl alcohol with propylene glycol as plasticizer, aspartame as sweetner, citric acid as saliva stimulating agent and water as solvent. The drug release for the formulations (F1 –F4) which contains 400mg of HPMC E-15, HPMC K-15, HPMC K-100, and PVA drug release was about 84.34; 96.55; 83.96; 94.28 respectively and for the formulations (F5 –F10) which contains the drug release was about 102.15; 96.55; 79.20; 88.64;95.47; 96.37 respectively. Cetrizine Dihydrochloride is freely soluble in water. Based on the *in-vitro* disintegration time, formulation F2 and F5 were found to be promising and showed a disintegration time of 20 and 18 sec respectively. However this FDF is useful for the improving of the bioavailability of the drug.

KEYWORDS: Cetrizine Dihydrochloride, FDF, Solvent Casting Method, *In-vitro* Study.

INTRODUCTION

Amongst all the established routes of drug administration, the oral route is perhaps the most preferred for both patients and healthcare providers compared to other routes such as

injections. However, this route of administration has disadvantages including enzyme degradation within the gastrointestinal tract which prohibits oral administration of certain classes of drugs such as peptides and proteins. Evidence has shown that the oral mucosa is relatively permeable with a rich supply of blood and shows a short recovery time after stress or damage. Further, it also lacks Langerhans cells which allow the oral cavity to be tolerant of any potential allergens.[1] Drug administration within the oral mucosa is generally classified into sublingual and buccal delivery. Amongst all the trans-mucosal routes, the buccal mucosa has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for the administration of retentive dosage forms.[2,3] Direct access to the systemic circulation through the internal jugular vein bypasses hepatic first-pass metabolism leading to relatively high bioavailability compared to the GI tract. Additionally, the buccal mucosa has a high surface area (50.2 cm^2) and a thin membrane (500–600 μm) which can contribute to rapid and extensive drug absorption.[4] Oral drug delivery systems have always been an important means of drug administration; however, many paediatric patients resist solid dosage forms such as tablets due to the bitter taste and fear of choking. Though sweetened liquid formulations are commonly used, they present many challenges including bitter after taste, unpleasant flavours, short half lives once opened and generally bulky to handle and store. Oral thin films offer easy administration and handling, rapid disintegration and dissolution, bypass first pass metabolism, enhanced stability and taste masking for bitter drugs, local and systematic drug delivery, rapid onset of action and no trained or professional person is required for paediatric administration.[5] Due to the numerous advantages of buccal dosage forms, various technologies have been explored to manufacture oral films on a large scale as an alternative to traditional dosage forms such as tablets and capsules.[6] Numerous buccal delivery systems in the form of tablets, liquids and semi-solids have been reported in the past decades, yet only a limited number of these have reached the market.[7] The necessity of recurrent dosing might possibly arise due to the flushing activity of saliva, chewing and the ingestion of food materials which results in the rapid expulsion of drugs. Moreover, the drugs in the saliva may be unevenly distributed, which might consequently lead to lower amounts being absorbed by the mucosal tissues directly into the systemic circulation. Furthermore, the likely displacement of the formulation from the buccal area by tongue movements serves as an additional challenge.[8] The above notwithstanding, the buccal mucosal route is still considered a practical route to deliver a variety of active ingredients. Hydrophilic polymers incorporating several hydrogen bonding groups make the formulation of bioadhesive buccal formulations feasible. Modified forms of such hydrogel polymers with better bioadhesivity

create second-generation mucosal dosage forms.[9] In the present study, we report on the development of solvent cast films for buccal delivery in paediatric patients using various hydrogel polymers generally regarded as safe (GRAS) and used in mucosal formulations[10–13] including HPMC E-15, HPMC K-15, HPMC K-100, PVA. Various parameters such as drying times and temperatures, casting solvents as well as polymer and plasticiser concentrations were investigated and the films subsequently characterised as part of the development and optimization.

EXPERIMENTAL

MATERIALS AND METHODS

Cetrizine Dihydrochloride was obtained as a gift sample from Swapnroop Drugs and Pharmaceuticals', Aurangabad. HPMC E-15, HPMC K-15, HPMC K-100, PVA, Propylene glycol, Citric acid, Aspartame were obtained from cipla pharmaceuticals, goa. All the chemicals were of analytical grade.

In the present study, mouth dissolving films of Cetrizine Dihydrochloride were prepared by solvent casting method, which involved the following steps: preparation of casting solution (containing drug, plasticizer, sweetener and flavor) as solution -1st and take another solution-2nd in which mix solvent (water) and polymer to make a homogenious solution with the help of magnetic stirrer, mix well both the solution (remove bubble from both the solution after mixing) and deaeration the solution, transfer of appropriate volume of solution into a mould, drying the casting solution by keeping on room temperature for 24 hours then cutting the final dosage form into strips (size 2x2 cm) to contain the desired amount of drug, packaging and storage. Different formulations were developed by varying polymer (HPMC E-15, HPMC K-15, HPMC K-100 and PVA.) and plasticizer (propylene glycol) concentrations. Sweetening and flavoring agents were added to make the formulation palatable. The films were evaluated for thickness, folding endurance, weight variation, disintegration time, dissolution time and drug content.

Table No.1:- Formula of the Cetrizine Dihydrochloride Fast Dissolving Film.

Ingredient(mg/ml) Formulation	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**	**F_{10}**
Cetrizine dihydrochloride	40	40	40	40	40	40	40	40	40	40
HPMC E 15	400	-	-	-	200	200	200	-	-	-
HPMC K15	-	400	-	-	200	-	-	200	200	-

HPMC K 100	-	-	400	-	-	200	-	200	-	200
PVP	-	-	-	400	-	-	200	-	200	200
Propylene glycol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Citric acid	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aspartame	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Amaranth	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

EVALUATION OF FAST DISSOLVING FILMS:

Weight variation: For weight variation three films of every formulation were taken weighed individually on digital balance then average weight was calculated. Film thickness: The thickness of each film was measured using micrometer screw gauge at different positions of the film and the average was calculated.[13]

Surface pH: Film is slightly wet with the help of water. The pH is measured by bringing the electrode in contact with the surface of the oral film. This study is performed on three films of each formulation and means ± S.D calculated.[14]

Folding endurance: The folding endurance was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.[15]

Drug content: A film of 2×2cm was cut and dissolved in 100ml of pH 6.8 and filtered. The contents were transferred to a volumetric flask (100ml). The drug is determined spectroscopically after appropriate dilution. Disintegration time: Disintegration test was performed in the USP disintegration time testing apparatus. One film from formulation was introduced into the tube of disintegration apparatus IP. A disc was added into the tube. The assembly was suspended in 0.5%SLS and operated until the film disintegrated.

In vitro dissolution studies: In-vitro dissolution of fast dissolving film was studied in USP paddle dissolution test apparatus using phosphate buffer pH 6.8 as the dissolution medium. The temperature was maintained at 37±0.5ºC throughout the experiment. 5ml Sample was withdrawn at 60sec intervals and the same quantity was replaced with phosphate buffer of pH 6.8. The cumulative percentage of drug released was determined using UV visible spectrophotometer at 231 nm.

Stability studies: The purpose of the stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety

of environmental factors such as temperature, humidity and light, enabling recommended storage condition, re-test periods and shelf life. The stability studies were carried out as per International Conference of Harmonization (ICH) Guidelines. Stability studies were carried out at 40º C / 75% RH for 3 months. The optimized film formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 40ºC / 75% RH for 3months and evaluated for their physical appearance, drug content and in-vitro dispersion time at specified intervals of time.

Table No.2:- Evaluations taste of Formulations from F1 toF10.

Formulations	Tack Test	Appearance	Weight mean (mg)	Thickness mean (mm)	Folding Endurance mean	D.T. mean (sec)	Surface pH	Cont.uniformity (%)
F1	Non tacky	Transparent	25	1	210	25	6-7	95.5
F2	tacky	Transparent	12	0.6	218	20	6-7	99.8
F3	Non tacky	Transparent	30	0.8	236	28	6-7	95.8
F4	Non tacky	Transparent	16	1.2	242	19	6-7	96.8
F5	Non tacky	Transparent	14	0.6	281	18	6-7	101.9
F6	Non tacky	Transparent	20	1.2	215	26	6-7	98.4
F7	Non tacky	Transparent	18	1	217	30	6-7	97.5
F8	Non tacky	Transparent	22	0.8	225	19	6-7	95.5
F9	Non tacky	Transparent	15	1	234	21	6-7	96.4
F10	tacky	Transparent	17	0.8	247	20	6-7	96.5

Table No.3:- Drug release profile of formulations from F1 to F10

Time(min)	% Drug release									
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
1	23.53	19.49	15.44	22.72	34.05	23.53	14.23	19.08	22.32	24.75
2	38.23	26.07	21.19	32.96	43.14	34.18	18.76	24.04	30.94	34.59
3	47.34	31.88	27.78	33.98	55.52	43.27	27.37	33.08	44.46	39.64
4	51.65	39.33	33.60	44.27	61.89	55.65	34.79	41.75	57.65	45.93
5	63.66	47.24	44.30	52.60	74.37	62.02	44.29	46.43	71.32	55.08
6	70.89	58.01	51.83	64.22	80.84	68.02	51.41	51.95	80.27	67.92
7	80.17	68.44	62.22	81.56	84.52	84.58	58.16	59.92	85.50	75.98
8	81.82	80.15	67.82	85.24	89.53	89.08	68.19	68.34	91.63	84.89
9	83.48	93.53	73.05	89.75	94.36	94.02	76.24	77.20	94.15	93.04
10	84.34	96.55.	83.96	94.28	102.15	96.55	79.20	88.64	95.47	96.37

RESULTS AND DISCUSSION

In present research work, an attempt has been made to prepare mouth dissolving films of Cetrizine Dihydrochloride by solvent casting method. The possible interaction between drug and excipients used in the formulation development of Cetrizine Dihydrochloride was studied by FTIR spectroscopy. The FT-IR spectra of pure drug and drug + excipients are shown in

Fig. 1. The FTIR spectrum of Cetrizine Dihydrochloride pure drug exhibited characteristic broad absorption band at 3406 cm^{-1} representing the presence of OH group (OH stretching). The aromatic C-H stretching and aliphatic C-H stretching bands were appeared at 2924 cm^{-1} and 2860 cm^{-1} respectively. Whereas a characteristic absorption band at 1680 cm−1 is due to the presence of C=O stretching.

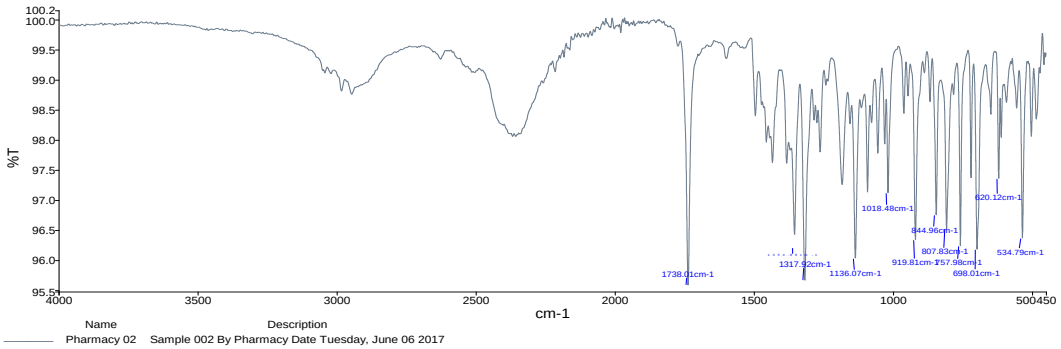

Fig. No. 1: FTIR Spectra of Cetrizine dihydrochloride.

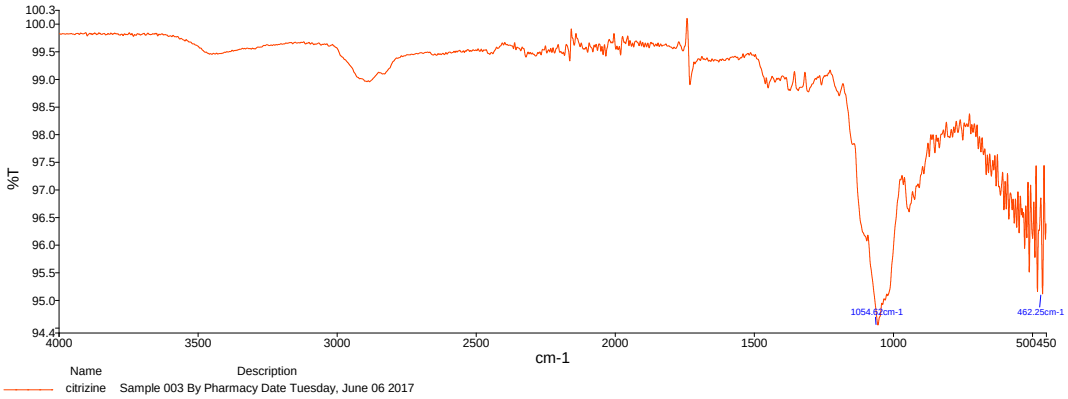

Fig. No.2: FTIR Spectra of HPMC E-15.

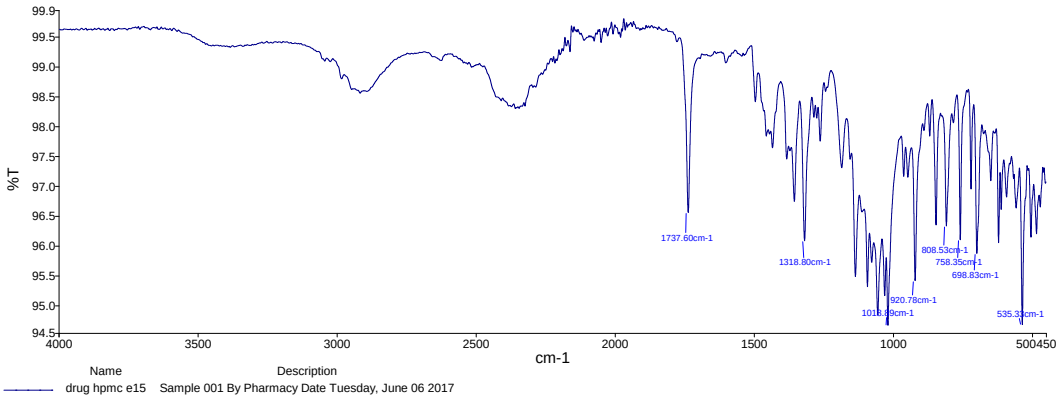

Fig. No.3: FTIR Spectra of Cetrizine dihydrochloride, HPMC E-15.

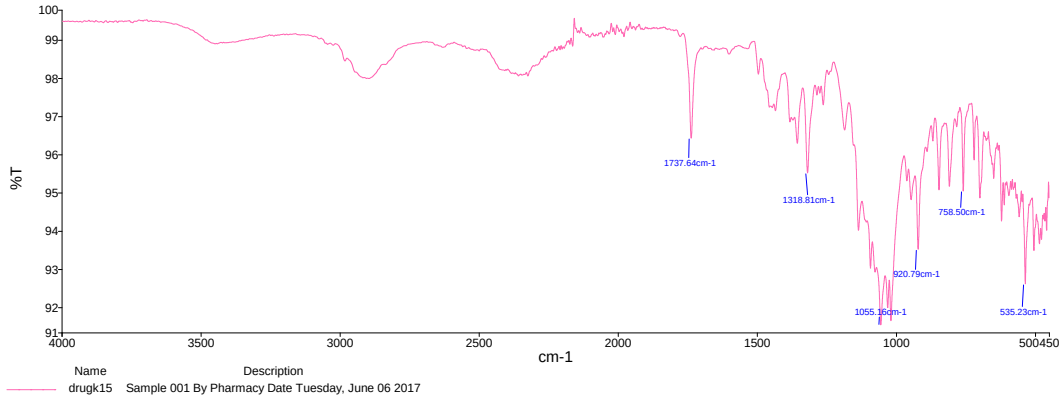

Fig. No.4: FTIR Spectra of Cetrizine dihydrochloride + HPMC K-100.

FIG 1-4: FTIR SPECTRA OF CETRIZINE DIHYDROCHLORIDE PURE DRUG AND EXCIPIENTS

Similarly the IR spectrum of Cetrizine Dihydrochloride and other polymers namely HPMC E-15, HPMC K-15, HPMC K-100, PVA showed characteristic absorption bands for the functional groups OH, Aromatic CH=CH, aliphatic CH=CH and C=O at or near that of Cetrizine Dihydrochloride absorption bands values indicating that there was no chemical and physical change in the functional groups present in Cetrizine Dihydrochloride.

EVALUATION TASTES

Physical appearance and surface texture: The appearance of all the films were uniform having transparent in appearance the observation suggests that the films were having smooth surface and they were elegant enough to see.

Weight uniformity of films: The weight of the prepared films was determined by using digital balance. All the films were tested for uniformity of weight and the results are given in Table 2. In all the cases the standard deviation values are very low which suggest the prepared films were uniform in weight.

Thickness of the films: All the films have uniform thickness throughout. In all the cases the standard deviation values are very low which suggest the prepared films were uniform in thickness. The results are given in Table 2.

Folding endurance: The folding endurance was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance. The folding endurance of all the formulations was in the range of 211 to 281 results was given in Table 2.

Surface pH of films: The surface pH was found to be in the range of 6 to 7 which is close to salivary pH, which indicates that films may have less potential to irritate the oral mucosa, thereby they are comfortable. The results are given in Table 3.

Drug content uniformity of films: The drug content of all the films was in the range of 95.54 to 102 % suggesting that drug was uniformly dispersed throughout all films.

In-vitro disintegration time of films: The In-vitro disintegration time of films prepared with HPMC was in the range of 10.00 to 30.00 sec. As the concentration of superdisintegrants increases the *in-vitro* disintegration time of the films decreases. Based on the in-vitro disintegration time, formulation F2, F5, F6, F9 and F10 were found to be promising and showed a disintegration time of 20, 18,21 and 20. Sec respectively. The results are given in Table 2.

In-vitro Dissolution Study: *In-vitro* dissolution studies of the prepared films were performed in pH 6.8 using USP type II (paddle) dissolution apparatus. The dissolution studies were conducted in triplicate in using Ph 6.8 solution as dissolution medium. The plot of % Cumulative drug release verses time (min.) were plotted and shown in table no.3. The dissolution rate was found varied with increasing concentration of superdisintegrant.

The drug release for the formulations (F1 –F4) which contains 400mg of HPMC E-15,HPMC K-15, HPMC K-100 and PVA drug release was about 84.34;96.55; 83.96; 94.28 respectively and for the formulations (F5 –F10) which contains the drug release was about 102.15; 96.55; 79.20; 88.64;95.47; 96.37respectively.

CONCLUSION

In present research work, an attempt has been made to prepare mouth dissolving films of Cetrizine dihydrochloride by solvent casting method. The fast dissolving films of Cetrizine Dihydrochloride were prepared by solvent casting technique using film forming polymer HPMC E-15, HPMC K-15, HPMC K100, PVA. Cetrizine Dihydrochloride is freely soluble in water. Based on the *in-vitro* disintegration time, formulation F2 and F5 were found to be promising and showed a disintegration time of 20 and 18 sec respectively. However this FDF is useful for the improving of the bioavailability of the drug.

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