

HPMC/CMC Based Fast Dissolvable Oral Films of an Anxiolytic: *In Vitro* Drug Release and Texture Analysis

Anoop Kumar¹, Pankaj Kumar Sharma², Asghar Ali³

*Corresponding author:

Anoop Kumar

1. Department of Pharmaceutical Technology,
Meerut Institute of Engineering & Technology,
NH-58, Meerut, Uttar Pradesh, INDIA

2. RajKumar Geol Institute of Engineering & Technology, 5th K.M. Stone, Delhi Meerut Road, Ghaziabad, Uttar Pradesh, INDIA

3. Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, New Delhi, INDIA

Abstract

Film forming capacity of a polymeric combination consisted of HPMC/CMC was investigated for fast dissolvable oral films (FDOFs) of an anxiolytic agent. Other non-film forming components were cross-povidone as disintegrant, and polyethylene glycol 400/ sorbitol in the ratio (1:1) as plasticizer, citric acid as saliva stimulating agent. Buspirone hydrochloride was selected as low dose anxiolytic agent with less than 5% oral bioavailability. Solvent casted films were physically evaluated for thickness, drug content, surface pH, swelling, disintegration and *in vitro* drug release. Mechanical properties of film viz. % elongation, tensile strength, Young modulus and elongation at break were determined using TXT texture analyzer. Drug loaded film (2.0 x 2.0 cm² size, average weight 60-70 mg) had average thickness in the range of 100-300 μ m. Higher HPMC/CMC ratios resulted in lower folding endurance in films (100 turnings), shorter disintegration time (10 sec) and simulated swelling time of 15sec whereas films produced at lower HPMC/CMC ratios had affected film characteristics conversely. Mechanical properties of film were found to relate the plasticizer ratio. Folding endurance and tensile strength of the films prepared at higher PEG 400/sorbitol ratios, showed comparatively higher values than film prepared at lower ratio. It had also been determined that higher ratios of PEG400/sorbitol were of shorter disintegration time. No drug-exipient interaction was observed from characterization studies conducted on films using FTIR and DSC methods. Films were stable at 30 \pm 0.5 $^{\circ}$ C; 60 \pm 5% RH. *In vitro* drug release showed that BH was released from film within ten minutes. It can be inferred that polymeric blend HPMC/CMC can be employed as fast dissolving oral film of BH for immediate release.

Keywords: Fast dissolvable oral film (FDOF), Oral film, Buspirone Hydrochloride, HPMC/CMC, Plasticizer

Introduction

Wide acceptance and competitive dominance of oral solid dosage form can be ascribed as the cumulative advantages offered by two biopharmaceutical parameters, i.e. selection of route of administration and dosage form. Oral ingestion is the most amicable, non invasive and highly preferred for systemic availability of drug as it offers several advantages e.g. ease of administration, minimal discomfort and avoidance of certain issues e.g. sterility. Similarly, solid dosage form has more benefit-risk ratio, improved patient compliance, precise control over dose delivery, enhanced drug stability etc. However oral solid dosage forms have certain limitations like difficulty in swallowing, sufficient fluid intake, unacceptability among pediatric and geriatric population associated with fear of choking of dosage form [1-2]. Moreover, the efficacy of orally administered solid dosage form is significantly hampered due to pre-systemic metabolism may result in poor absorption of drug [3].

Clinical effectiveness of new immediate release (IR) systems is well evident over conventional products. Among these systems,

mouth dissolving films, oral patches and wafers has been shown more efficacious use of drug. Fast-dissolving oral films (FDOF) are the safe and clinically more effective than conventional dosage form [4]. Usefulness of FDOF has been investigated in certain chronic diseases like e.g. depression, emesis [5-7]. FDOFs allow taste masking, facilitating quick disintegration or dissolution in saliva and can be swallowed without intake of water [8]. However its mechanism is yet to be established however it has been proposed that drug released is itself absorbed from mouth cavity. FDOFs synonymously called as oral strip technology (OST) or mouth dissolving films, fast disintegrating films used by non-prescription OTC medication. Solvent casting, molten state blending, spraying and spreading are few techniques employed in the fabrication of FDOF [9-10].

Buspirone hydrochloride is a low dose, HT₂-receptor antagonist, indicated for generalized anxiety disorder [11-12]. It has fair palatability and has high aqueous solubility, its structure is shown in figure 1. Low bioavailability (less than 5%) of BH is due to its extensive first pass metabolism following oral absorption [13].



A very few and limited number of film forming substances have been explored in the development of FDOFs. Pullulan, a natural polysaccharide obtained from sucrose fermentation in fungal strains *leuconostoc mesentroid*, have been widely explored as film former in FDOF. Although, film forming potential of pullulan is well appreciated for mechanical and physical properties however issues on economical aspects has been raised [14]. Film forming capacity of maltodextrin has also been undertaken however more dissolution time is the major constraint. Therefore, exploration of new polymeric film formers would be needed and their usages were already in pharmaceutical excipient. Film formation characteristics of HPMC had been investigated in oral strip technology [15-17]. More recently, nanoparticles of BCS class II drug was embedded in HPMC based oral films and it resulted in significant improvement in dissolution characteristic of drug [18]. Moreover HPMC showed film formation in combination with PVA and the developed film from polymeric combination exhibited good film formation which can hold sufficient mechanical strength [19]. CMC has been shown to produce rapid disintegration in aqueous based film coating and comparable to PVA [20].

The present investigation aims to explore film formation capacity of HPMC/ CMC blend for fabrication of FDOFs of BH using solvent casting method. The effect of plasticizer on mechanical properties of FDOF was evaluated.

Materials and Methods

Hydroxypropylmethylcellulose (E5, viscosity grade; 5mPas) and sodium carboxymethylcellulose (low viscosity grade) were kindly provided by Signet Chemical Corporation, Mumbai, India. Cross povidone, sorbitol, polyethylene glycol 400 (PEG 400) and citric acid were procured from SD fine chemicals (P) Ltd, Mumbai, India. Buspirone hydrochloride (BH) was obtained from Sigma. All other chemicals and reagents used in this study were of analytical grade and used as received without any attempt to further purify the same.

Fabrication of films

Drug loaded HPMC/CMC films were prepared using solvent casting method. In brief, aqueous polymeric solution was prepared by dissolving specified quantity of polymers in distilled water, and was mixed under stirring for two hours with specified quantities of plasticizer and disintegrant in table 1. In another container, aqueous solution (0.5ml) containing drug and saliva stimulant agent was dissolved. Both solutions were stirred for two hours and allowed to stand overnight under vacuum and made free from entrapped air. Solution was spread uniformly with the help of spreader on polyvinyl tile placed over flat surface avoid rinsing. It was overnight dried at ambient temperature. Films of desired size was cut with the help of sharp knife, packed and stored in an air tight, light resistant container.

Characterization of Films

FTIR

FT Infrared spectra of drug loaded and placebo films were analyzed at frequencies 400-4000 cm^{-1} using Shimadzu, FTIR Spectroscopy 8002. Dried films were placed vertically in sample holder assembly of the instrument directly and the spectrum was recorded whereas spectrum of drug was recorded using standard KBr pellet method.

DSC

Thermal characterization of film was ascertained by differential scanning calorimetry using Perkin Elmer, Calorimeter US. Film sample (approx 20 mg) crumbled in sealed aluminum pan were placed into sample holder and scanned at heating rate 5 C/min in nitrogen environment. Different thermal events were recorded in the temperature range of 50 to 350 C with calculation of heat of fusion.

Physical Evaluation of Film

Dimension Measurement

An average thickness of three films was measured. Thickness was measured at six different points from each film using digital coordinate measuring machine, Mitutoyo, Japan. Least count was 0.01mm.

Folding Endurance

Folding endurance was determined manually using simple method consists of folding at the vertical axis of film repeatedly. Number of folds required to break the film into two halves is counted as folding endurance.

Drug Content

Six samples were cut accurately equivalent area of 2.2 cm^2 from each batch of film and were dissolved in 0.1N HCl (10.0 ml) of volumetric container. Resulting solution was sonicated for half an hour and filtered through membrane filter. Absorbance was determined at λ_{max} of 235.0 nm using double beam UV/Vis spectrometer model, Shimadzu, 1800. Drug content was calculated from standard curve drawn between known concentrations of drug vs. absorbance of solution.

Surface Ph

Aqueous solution of films was diluted and pH of solution was determined by pH meter.

Disintegration Time

Disintegration of film was determined in phosphate buffer pH 7.0 using disintegration test apparatus. The time required (in seconds) to disintegrate the film was noted till mass of film was dispersed uniformly in the phosphate buffer pH 7.0 containing water soluble dye.

Swelling Time Simulation



Time required to completely swell the film was determined by swelling time simulation method. A small plastic mesh frame (3.0 3.0 cm²) was placed in a petri plate (internal diameter is 6.5 cm) containing 1.0 ml of water maintained at 37 C. Film was placed on the mesh frame previously dipped into the water and the time required to wet the film was noted (in seconds). Simulated swelling time corresponds to the time taken by the film to disintegrate under simulated conditions when films were kept over the tongue.

In Vitro Drug Release

In vitro drug release from films was determined at 37±0.5 C at 50 rpm using 100 ml of 0.1N HCl as a dissolution medium (n=3) in USP XXIV type-2 apparatus (Electrolab, TDT-06T, India). Samples (5.0ml) were withdrawn from from dissolution medium at predetermined intervals at 0.5, 1, 2, 4, 8, 10 and 15min. Equal volume of fresh medium of identical temperature was replaced in dissolution vessel. Samples were filtered through a (0.45µm) membrane filter, followed suitable dilution and analyzed spectrophotometrically at λ_{max} 235.0nm. Amount of dissolved drug was calculated from standard curve drawn between absorbance of known concentrations of drug.

Texture Analysis of film

Texture properties of the films were evaluated using TA.XT Plus, Texture Analyzer, Stable Microsystem, UK. Texture properties of films were determined using attachments TA-96B: tensile grip fixture (grip distance 30mm; and grip displacement rate (0.01mm/sec) at 5N load cell. Following mechanical properties of each film sample were determined in triplicate.

% Elongation

Percentage elongation of films was calculated by dividing the extension of original length of film to original length of the film.
% Elongation of film = (Extension of film length / original length of film) 100

Tensile Strength

Tensile strength of film was calculated from the applied load tends to break the film dividing its original cross- sectional area. The result is expressed in g/ cm² and reported to three significant figures.

Tensile strength= (Applied load at which film break/ width thickness of film) 100

Elastic Modulus

The slope of linear portion of force-displacement upward curve was measure of elastic modulus of film. Its units is in kg mm⁻¹

Elastic Modulus of film = Linear force applied on film / displacement of film

Elongation At Break

The area under force-displacement upward curve was the measure of tensile energy at break.

Stability of Film

Dynamic Vapor Sorption

Dynamic vapor sorption studies of film was assessed by placing films at controlled humidity conditions maintained at 40, 50, 60, 70 and 75 ±5% RH prepared by saturated salt solutions in humidity desiccators at 25 C. Films (2 2 cm²) were warped in the aluminum foils and placed in humidity containers and the change in weight of FDOFs after a month period of storage was determined.

Assay

Films were subjected to storage at 25 ±0.5 C, 60 ±5% RH and assayed for BH after a month.

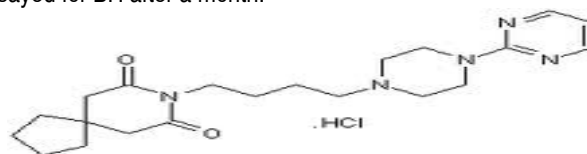


Figure 1: Structure of Buspirone hydrochloride (8-[4-(4-pyrimidin-2-yl)piperazin-1-yl]butyl]-8-azaspiro[4.5]decane-7,9-dione)

Table 1: Composition of different drug loaded film formulations

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
HPMC E-15 (mg)	350	350	350	350	350	350	400	400	400	400	400	400
CMC (mg)	25	50	100	25	50	100	25	50	100	25	50	100
Citric acid (mg)	20	20	20	20	20	20	20	20	20	20	20	20
Sorbitol (mg)	20	20	20	40	40	40	20	20	20	40	40	40
PEG 400 (mg)	20	30	50	20	30	50	20	30	50	20	30	50
Crospovidone (mg)	20	20	20	20	20	20	20	20	20	20	20	20
BH (mg)	40	40	40	40	40	40	40	40	40	40	40	40
HPMC/CMC ratio	14	7	3.5	14	7	3.5	14	7	3.5	14	7	3.5
Sorbitol/PEG ratio	1.0	0.6	0.4	2.0	1.3	0.8	1.0	0.6	0.4	2.0	1.3	0.8

BH= Buspirone hydrochloride;

Results and Discussion

Film forming capacity of polymeric mixture consisting of HPMC / CMC as well as film plasticizing property of PEG400/sorbitol was investigated. Fast dissolvable film of buspirone hydrochloride was prepared at different combinations of HPMC/CMC using solvent casting method and physical and mechanical properties of the developed films were assessed. Films prepared from HPMC alone were reported to have good mechanical properties of film with variation in film disintegration was found to depend on disintegrant used [21]. Carboxymethylcellulose has shown good disintegration properties in buccal as well as conventional tablets and has been employed in aqueous based film coating. Incorporation of CMC in polymers film formers e. g. HPMC might alter their physico-mechanical properties of films. Composition of drug loaded films showing quantities of film formers, plasticizers, disintegrants and saliva stimulating agent are given in table 1. Several preliminary trials were conducted to fix the amount of disintegrating agent in film. Several preliminary studies showed that quick disintegration of film (20secs) was achieved when fixed quantity of disintegrant (20mg) was added to film. The aim of present study was to investigate film forming capacity of HPMC/CMC and to evaluate

the physical and mechanical properties of BH loaded FDOF at different levels of plasticizer (sorbitol/PEG400). Films were visually inspected for integrity, sign of cracks or layering on the surface of films and evaluated for thickness, uniformity of drug content and film weight, folding endurance, disintegration time and simulated time of swelling.

Evaluation of film characteristics

Films prepared at different polymeric combinations of HPMC/CMC and plasticizers ratio were evaluated for average weight, thickness, folding endurances of films as shown in table 2. Variation in drug content, weight of film and film thickness was corresponded to viscosity of polymeric film formers. Folding endurance of film is a rough qualitative measure of mechanical properties of film was related amount of film former, plasticizer added in film. Films prepared at selected ratios of film formers and plasticizers, did not show any sign of break or crack in films and found to be unbreakable upto 100 to 300 folds. It is indicated from the results that the films were rapidly disintegrable and hold sufficient mechanical strength against transportation and handling.

Table 2: Evaluation of physical parameters, texture and stability characteristics of different film formulations

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
PHYSICAL CHARACTERISTICS												
Film thickness* (μm)	100	103	110	121	119	122	115	109	108	126	135	115
Average weight*** (mg)	62	65	63	64	62	62	64	68	66	64	61	65
Drug content** (mg/cm ²)	0.97	0.98	0.99	0.95	0.96	0.94	0.93	0.90	0.97	0.90	0.90	0.98
Surface pH	6.8	6.8	6.9	6.9	6.9	6.8	6.8	6.9	6.9	6.9	6.8	6.9
Disintegration time** (sec)	8 \pm 2	8 \pm 1	9 \pm 1	10 \pm 2	10 \pm 3	10 \pm 2	11 \pm 2	11 \pm 3	12 \pm 2	12 \pm 1	14 \pm 2	14 \pm 3
Swelling time simulation**	15 \pm 1	15 \pm 2	15 \pm 2	17 \pm 2	17 \pm 2	20 \pm 1	20 \pm 1	20 \pm 2	17 \pm 1	25 \pm 2	20 \pm 1	17 \pm 2
Mean dissolution time ⁺ (min)	3 \pm 2	4 \pm 2	5 \pm 2	9 \pm 2	10 \pm 1	6 \pm 1	4 \pm 3	5 \pm 2	10 \pm 1	13 \pm 2	13 \pm 2	9 \pm 2
Folding endurance (%)	100	108	130	200	210	230	204	210	158	320	351	298
TEXTURE ANALYSIS												
Elongation (%)	0.75	0.85	1.52	2.5	2.7	3.0	2.59	2.75	2.15	3.4	3.7	3.2
Breaking force (g)	71.9	100.5	274.2	380.1	404	472	285	410	304	480	540	415
Energy at break (g.mm 10 ⁻²)	1.58	1.79	7.901	13.58	15.24	18.10	18.15	16.33	8.52	19.10	22.46	15.40
Young modulus (kg/mm)	0.22	0.23	2.82	3.12	3.15	3.75	3.16	3.08	2.92	3.22	4.03	3.18
STABILITY PARAMETERS												
Film stability [¶] (weight %)	2.1	2.1	2.1	2.8	2.8	2.8	2.5	2.6	2.1	3.0	3.5	2.5
Drug assay (%)	99.7	99.5	99.7	99.6	99.6	99.6	99.5	99.5	99.4	99.5	99.1	99.5

* mean of ten measurements; ** mean of six determinations; □ means of three readings; *** size of 2.0 2.0 cm²; ¶ at 50% RH at 25C

Effect of polymer ratio

Film formation capacity of HPMC E 50 is well known and has been used in aqueous based film coating in tablets and sustained release products. Thermo-mechanical properties of HPMC based films have been investigated and were found to depend upon specific polymer grade, type and quantity of non-film former ingredients added to film and method employed in its preparation [22]. In the present study, thickness of films was increased at

lower HPMC/CMC ratio (Comparison of F7-F9 vs. F1-F3). During fabrication of films, it has been determined that increasing proportion of CMC in film former was resulted in higher viscosity of polymeric solution. Thickness of film obtained from solvent casting method depends on the viscosity of polymeric solution and produced comparatively less flexible films as shown in Figure 2. Films prepared at low HPMC/CMC ratio, had lower mechanical strength and were easily breakable as these films could not have much flexibility, low tensile strength and lesser energy at break as

observed in figure 3. Consequently films were easily disintegrable showed much faster drug release from films upon dissolution [23]. At higher HPMC content in polymeric blend, thickness of films was reduced due to lower viscosity of polymeric solution. Higher HPMC/CMC ratios produced more flexible films with increased mechanical strength as determined from percentage elongation, tensile strength and energy required to break. Conversely such

films showed much lower disintegration and swelling time. Difference in mechanical properties had been observed in films made from HPMC modulated by adding amount of CMC. Variation in film properties may be proposed to relate with polymeric entanglement of CMC with HPMC. Similar observations in physical and mechanical properties of FDOF were obtained when (F2-F5) were compared with (F10-12).

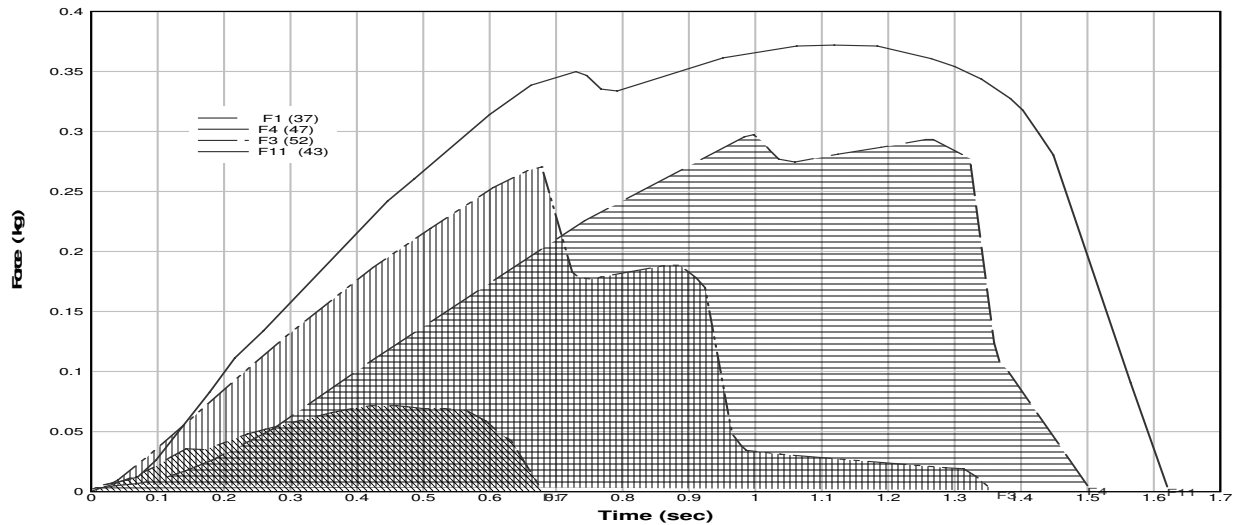


Figure 2: Force-time plot of representative formulations showing flexibility of film with respect to extension of films with time (F1, F3, F4 and F11)

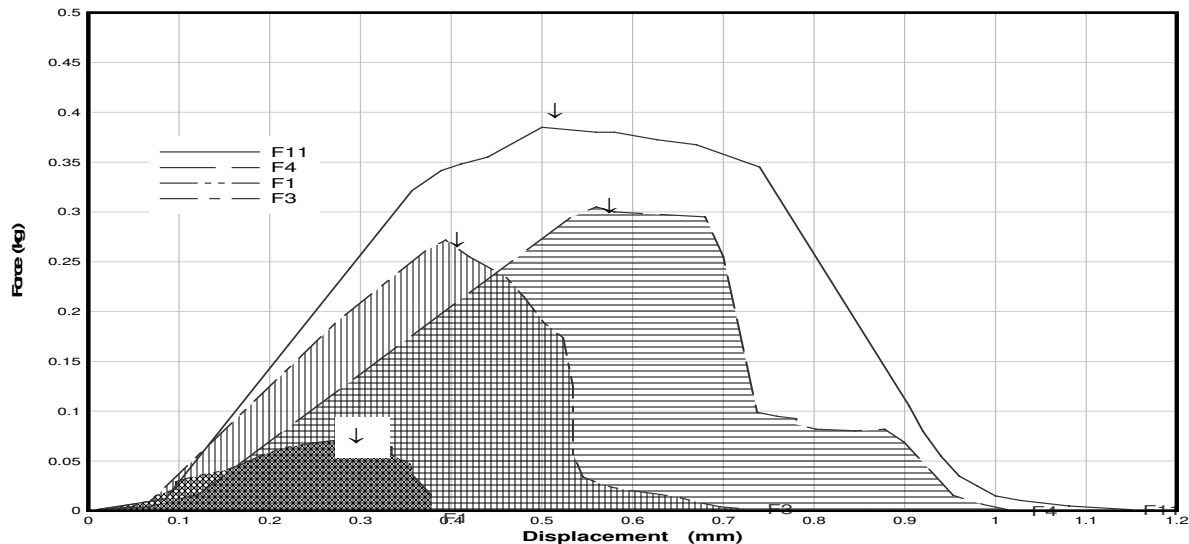


Figure 3: Area under the curve obtained from force-displacement plot of different representative film formulations (F1, F3, F4 and F11) (AUC of F3 =0.079; F11=0.2246; F1=0.01585; F4=0.135 kg. mm)

Effect of plasticizer ratio

Pronounced variation in films texture has been found to relate with amount of plasticizers incorporated in films rather than amount of films formers [24]. It has been shown that increasing amount of plasticizer produced more flexible films and modifies the texture of

films possibly due to ease in polymeric chain movements [25]. However incorporation of excessive quantity in films (PEG 600) could produce limiting effect on the physico- mechanical properties of HPMC based films [26]. Increasing amount of plasticizer would be resulted in lower tensile strength of film, thereby produce quick disintegration and dissolution of films. Hence in the present study,

the plasticizing effect of PEG 400 alone was modified using combination of sorbitol in the ratio (1:1). Films contained larger proportion of sorbitol as plasticizer at fixed level of film former (F1-F3) vs. (F4-F6) gave suffice mechanical strength to film as shown in table 2. It indicates from the results that incorporation of sorbitol as plasticizer to PEG 400 conferred more flexibility to films than PEG 400 alone. Plasticization property of sorbitol has been used in film coating of tablets. However, film prepared at larger HPMC/CMC ratio, increasing amount of sorbitol (F9-F12)

decreased the mechanical strength and texture properties as observed in F12 batch. Area under the force displacement curve of F4 batch was much higher than F1 indicates better film texture as it may be result from increased amount of plasticizer (figure 3). Above results showed that the films took more energy to fracture were comparatively tough and disintegrated comparatively slower and took much large dissolution time as shown in figure 4 and 5. Films were comparatively more elastic if they had higher Young's modulus [27].

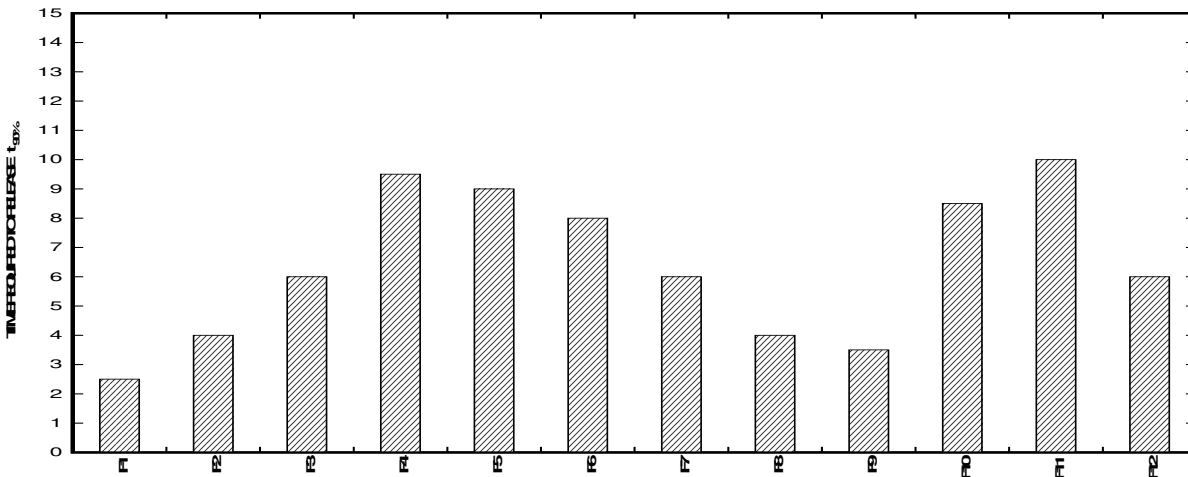


Figure 4: Time taken to release ($t_{90\%}$) from film formulations (F1 to F12) where $t_{90\%}$ is the 90% drug was released.

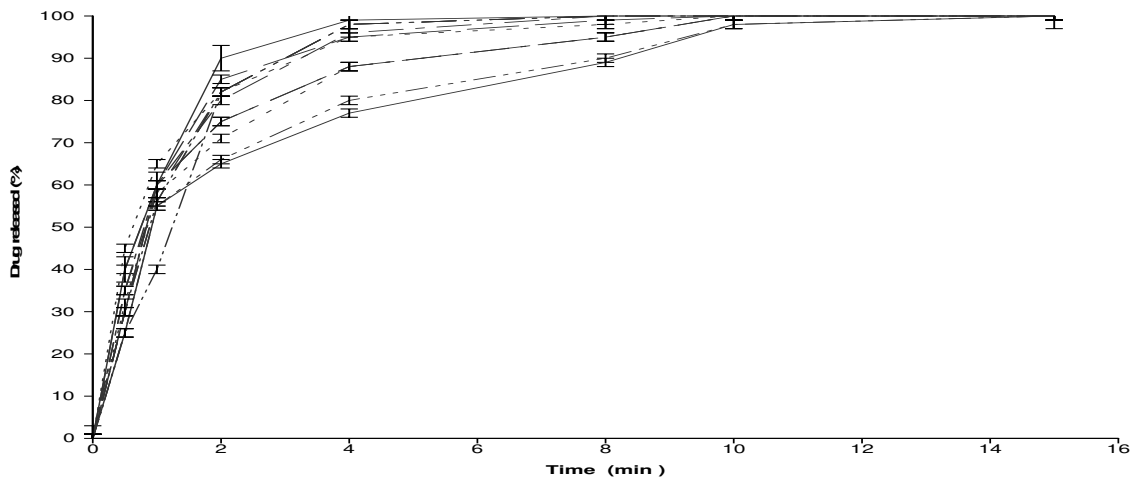


Figure 5 *In-vitro* drug release from various film formulations (F1 to F12)

Characterization of films

Films were characterized by FTIR spectroscopic method and were represented in figure 6. FTIR characterization revealed that films showed strong absorption bands at 2800 cm^{-1} resulted from aliphatic C-H group, stretching vibration at $1250\text{-}1330\text{ cm}^{-1}$ for aromatic amine and stretching vibration at 1722 cm^{-1} was due to C=O (ketone) groups and stretching at 1250 cm^{-1} for aliphatic C-N groups. FTIR spectra of FDOFs have had identical group

frequencies of BH. Thermal characterization was films performed using DSC studies and were represented in figure 7. DSC thermogram showed that no extra thermal event other than one melting endothermic at 200 C which corresponds to melting point of drug. On the basis of spectral and thermal characterization studies on films, no interaction between drug and the excipients in FDOFs had been observed.



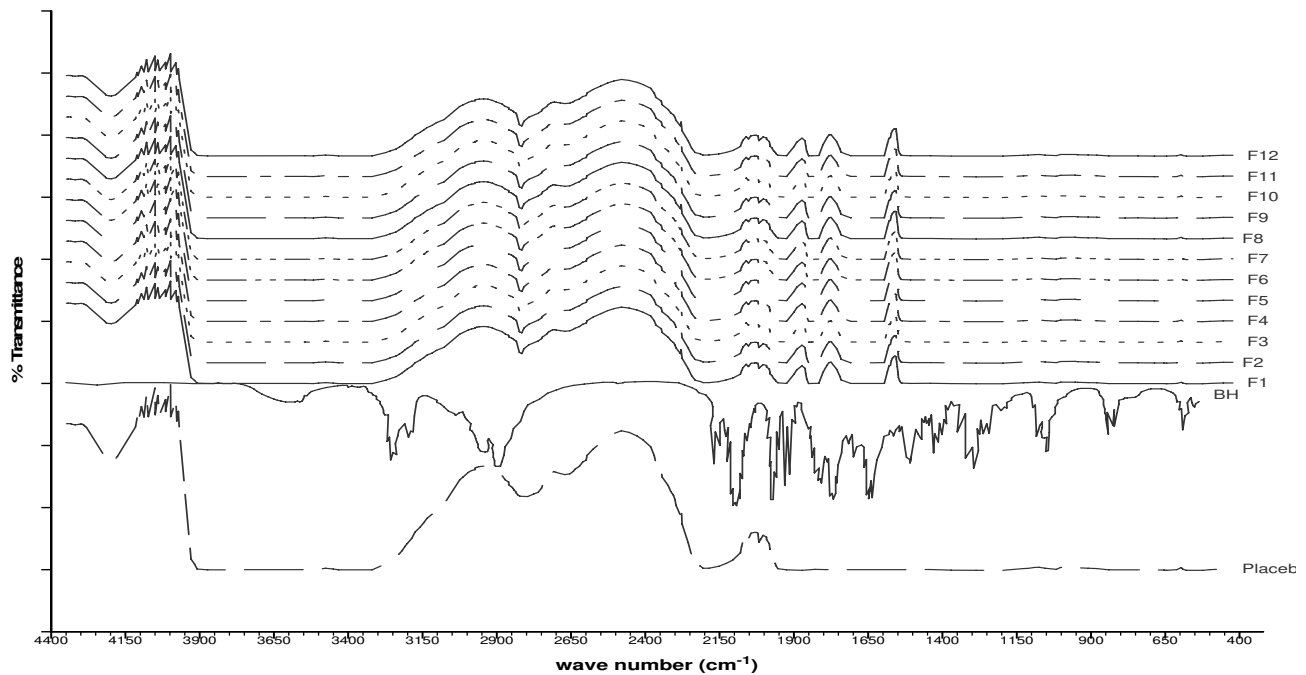


Figure 6: FTIR spectroscopic characterization of various film formulations (F1 to F12); drug sample (BH); placebo film (F11)

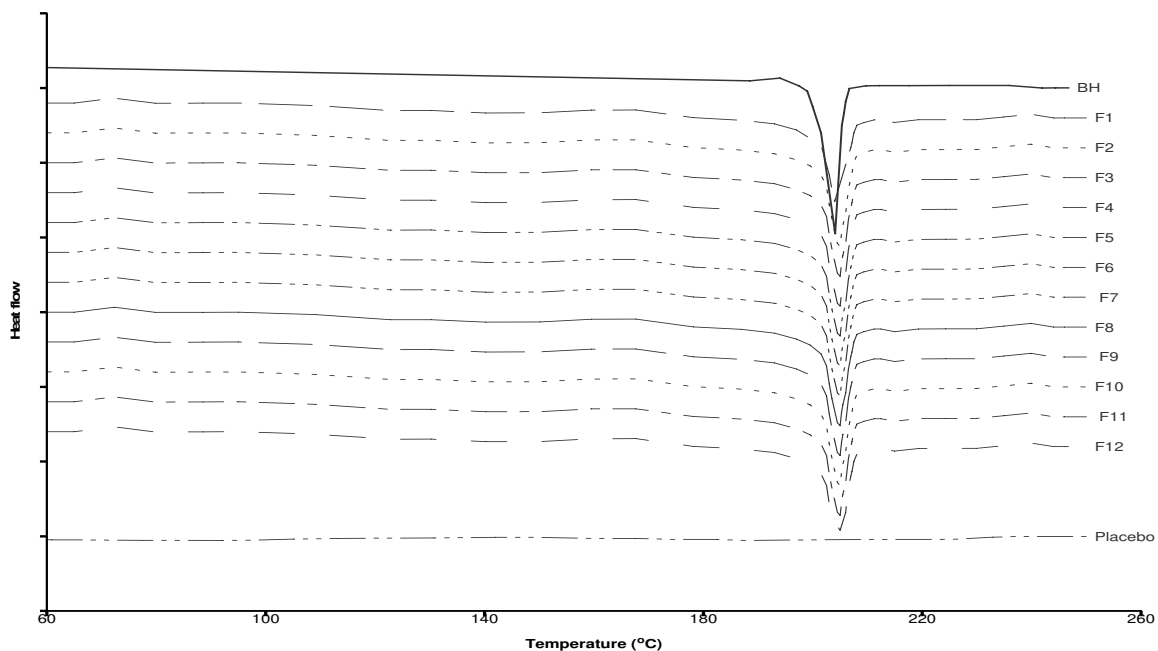


Figure 7: DSC thermogram of various film formulations (F1 to F12); pure drug (BH) and placebo film (F11)

Disintegration & In vitro drug release

In vitro drug release studies and disintegration test of films were carried out in phosphate buffer at pH 6.8 and its results were shown in figure 5. Mean disintegration time of films was found to be less than 14 seconds whereas its corresponding *in vitro* dissolution time was 600 seconds. Large dissolution time was

attributed to entanglement of drug in film base which mainly comprised of polymeric and plasticizing component. These components retard the drug release entrapped in its base. Though quick disintegration of film was take place at higher HPMC/ CMC ratios [23]. However the CMC has been used as and aid to disintegrant It resulted in enhancement of dissolution times for FDOF when compared with hydroxypropyl methyl cellulose based

films. Time required to completely moisten and swell the film was also lowered in case of film with low HPMC/CMC ratios.

Stability studies

Vapor sorption studies were carried out on films at different relative humidity levels and its effect on weight of FDOFs was given in table 2 and graphically represented in fig 8. No significant changes in the weight of films were observed when it was subjected for storage at controlled humidity conditions maintained. All FDOFs

formulations at these conditions were stable below 60%RH in integrity and strength irrespective of HPMC/CMC ratio [28]. However at low HPMC/CMC ratio, moisture sorption was comparatively large. Low moisture sorption had been observed at higher HPMC/CMC ratio. No significant change in assay of BH in the FDOF was observed after a month. Dynamic vapour sorption studies also revealed that films containing higher amount of CMC adsorb more water at humidity level above 60% RH. It would have been resulted in stickiness tendency of the films.

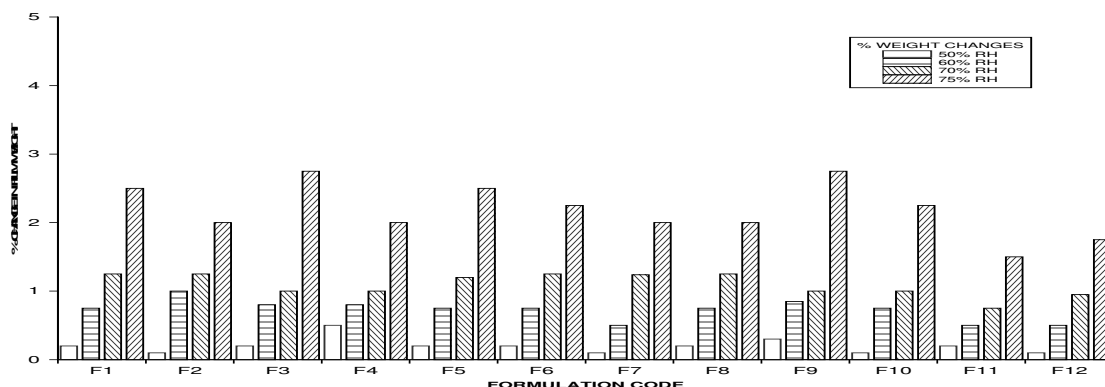


Figure 8 Vapor sorption studied conducted on film formulations at different humidity levels at 50, 60, 65 and 75% RH for a month and its effect on weight of films.

Conclusion

Film forming potential of a polymeric combination consisted of HPMC/CMC using solvent casting method was explored for fast dissolvable film of buspirone hydrochloride. FDOFs exhibited plausible features in fabricated films like texture and mechanical strength, physical and stability characteristics upto 65%RH. Quick disintegration of the FDOF within seconds can be related with

lower HPMC/CMC ratio and PEG400/sorbitol ratio however it took ten folds higher time for drug release. No interaction between drug and excipients was occurred in FDOFs. Film texture was found to be more related with the nature and quantity of plasticizer incorporated whereas thickness, disintegration and dissolution properties of FDOF was depend on film former ratio.

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