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Formulation and Evaluation of Fast Dissolving Oral Film Using Natural Polymer Pullulan

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ABSTRACT

Fast dissolving oral film was prepared by using pullulan as a film forming agent, glycerine as a plasticizer, Aspartame as sweetening agent. Solvent casting method was used for formulation of film. The 2 x 2 cm film is placed on tongue it get instantly hydrated by saliva ,adhere to tongue and rapidly disintegrate and dissolves to release the drug. The prepared films were also evaluated for their weight uniformity, thickness, surface pH, drug content, *in vitro* disintegration time, *in vitro* drug release, film stability and mechanical properties as folding endurance. The film thickness (mm) ranges from 0.021±0.0015 to 0.032±0.015 and the folding endurance ranges from 9.33±0.577 to 14.23±1.15 respectively. The drug content (mg %) was studied and it ranges from 97.04±1.08 to 99.07±1.02. Increase in the levels of Glycerin causes an increase in the Folding Endurance while Pullulan had a negative effect. A plasticizer has a negative effect on the Drug Release. % Drug Release of the film increased with decrease in levels of both polymer and plasticizer. All film having acceptable mechanical properties and the time required to disintegrate were within 25 second and total % drug release is in 5 min. Stability study of optimized Fast Dissolving Film of Buspirone hydrochloride was revealed for 3 month which shows no significant difference. This study revealed, successful formulation of Fast Dissolving Oral Film. The Fast Dissolving Oral Film showed highest drug release and average folding endurance. The high % drug release of the film in phosphate buffer pH 6.8 at 5 min indicated that these films can be real alternative to traditional OTC product like tablets and capsule.

Keywords: Fast dissolving oral film, film forming agent, plasticizer, Solvent casting method.

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INTRODUCTION

The concept of orally disintegrating dosage forms has emerged from the desire to provide patients with more conventional means of taking their medication. About 60% of all dosage form available is in the oral solid dosage form. Interestingly, the demand for ODT has enormously increased during the last decade, particularly for geriatric and pediatric patients who experience difficulty in swallowing conventional tablets and capsules. Hence, they do not comply with prescription, which results in high incidence of ineffective therapy.[1]

Conventional tablet formulations have acquired the 50 to 60 % market stake. According to this data, the tablet formulation is most popular form but with this tablet having acceptance problem in the patients suffering from dysphasia, Parkinson's disease, mycosystis or vomiting, geriatric, bed ridden, psychotics and paediatrics patient because unwilling to take solid preparations due to fear of choking.[2] One study showed that 26% of 1576 patients experienced difficulty in swallowing tablets. From the patient point of view fast dissolving film offers ease of administration and improved compliance.[3]

Buspirone hydrochloride is a low dose, HT2-receptor antagonist, indicated for generalized anxiety disorder. It has fair palatability and has high aqueous solubility. Low bioavailability (less than 5%) of Buspirone hydrochloride is due to its extensive first pass metabolism following oral absorption.[4]

Pullulan is a naturally occurring fungal polysaccharide produced by fermentation of liquefied corn starch Aureobasidium pullulans, ubiquitous yeast like fungus. It has been widely explored as film former in of Fast dissolving oral film.[5] Film forming capacity of maltodextrin has also been undertaken however more dissolution time is the major constraint.

The present investigation aims to explore film formation capacity of Pullulan blend for fabrication of Fast dissolving oral film of Buspirone Hydrochloride using solvent casting method. The effect of plasticizer on mechanical properties of Fast dissolving oral film was evaluated.

MATERIALS AND METHOD

Pullulan, Hydroxy propyl methyl cellulose E5, E6, E15, and Maltodextrin these film formers were kindly provided by Ajanta pharma, Mumbai. Glycerine, PEG 400(Plasticizers) was procured from Moly chem. Pvt. Ltd. Mumbai. Buspirone Hydrochloride was obtained from Unichem Laboratories, Goa, India. 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.

Methods:

Preparation of films with Pullulan:

All the ingredients were weighed accordingly. The Pullulan was dissolved in 6ml water. The drug and aspartame are dissolved in remaining water. The resultant solution is plasticized with using suitable plasticizer and stirred for 15 minutes to produce a clear solution, which kept aside for 15 minutes to get bubble free solution. These solutions were casted slowly and with continuous flow on glass plate to prevent formation of bubbles then it kept for drying. The dried film was gently separated from glass plate and evaluated.

Before final formulation trials were carried out with polymers HPMC E grades and Pullulan. Trial batches were evaluated further for the folding endurance, thickness, disintegration time and transparency. Table 1 and 2 shows the trial batches.

Table 1: Trial batches with Pullulan

Sr. No.	Trial code	Buspirone Hydrochloride(mg)	Pullulan (mg)	Glycerin (mg)	Aspartame (mg)
1	P1	92	200	30	30
2	P2	92	300	30	30
3	P3	92	400	30	30

Table 2: Trial batches with HPMC E grades:

Trial code	Buspirone Hydrochloride(mg)	HPMC E5(mg)	HPMC E6 (mg)	HPMC E15(mg)	Glycerin(mg)	Aspartame (mg)
$H5_A$	92	100	-	-	30	30
$H5_B$	92	200	-	-	30	30
$H5_C$	92	300	-	-	30	30
$H6_A$	92	-	100	-	30	30
$H6_B$	92	-	200	-	30	30
$H6_C$	92	-	300	-	30	30
$H15_A$	92	-	-	100	30	30
$H15_B$	92	-	-	200	30	30
$H15_C$	92	-	-	300	30	30

These formulated films of above polymers evaluated for folding endurance, thickness, disintegration time and transparency.

Table 3 Formulation design

Sr.No.	Ingredients(mg)	F1	F2	F3	F4	F5	F6
1	Bupirone Hydrochloride	92	92	92	92	92	92
2	Pullulan	200	300	400	200	300	400
4	Glycerin	30	30	30	-	-	-
5	Propylene Glycol 400	-	-	-	30	30	30
6	Aspartame	30	30	30	30	30	30
7	D.W.(ml)	10	10	10	10	10	10

** Area of the film- 2 X 2 cm,*** Dose of drug per film- 5 mg

Evaluation Parameters of Oral Fast Dissolving Film: [2, 4, 5]

Oral fast dissolving films of Buspirone Hydrochloride were evaluated for their morphology, weight, thickness, pH value, folding endurance, drug content, disintegration time, and in vitro dissolution. All studies were carried out in triplicate and average values were reported.

Weight of Films

Oral fast dissolving films were weighed on analytical balance and average weight can be determined for each film. It is desirable that films should have nearly constant weight. It is useful to ensure that a film contains the proper amount of excipients and API.

Thickness of Films

The thickness of the film was measured by micrometer screw gauge at three different places and average of three values was calculated**.** This is essential to ascertain uniformity in the thickness of the film which is directly related to the accuracy of dose in the film.

PH value:

The pH value was determined by dissolving one oral film in 10 ml distilled water and measuring the pH of the obtained solution. All determinations were performed in triplicate. It is necessary that strip should have nearly uniform pH value.

Folding Endurance

Folding endurance of the film is essential to study the elasticity of the film during storage and handling. The folding endurance of the films was determined by repeatedly folding one film at the same place till it broke. This is considered to reveal good film properties. A film (2 X 2 cm) was cut evenly and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance. All determinations were performed in triplicate.

Content Uniformity

Drug content was determined by dissolving the film containing 5 mg of drug in 100 ml water to get 50 µg/ml solutions. An aliquot of 0.5 ml sample was withdrawn and diluted to 10 ml with water. Then solution was filtered through whatman filter paper and analyzed by UV-spectrophotometer at 238 nm against blank prepared by using dummy film treated in same manner. Content uniformity studies were carried out in triplicates for each batch of the film. Regression equation and regression coefficient were calculated by using equation Y= mx + C where, (x= concentration µg/ml, Y= absorbance and m= slope), respectively.

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip breaks. In this test the

strip was tied between two clamps and the one end of clamp was directly attached to pan through pulley. The stress was applied to the strip by putting load in the pan and finally the reading of load at failure was noted. All determination was performed in triplicate with standard deviation. It is calculated by the following formula:

Tensile Strength =Force at break /Initial Cross Sectional area of film in mm^2

Disintegration Time

It was determined visually in a glass beaker filled with 25 ml distilled water with swirling every 10 seconds. The time at which film started to break or disintegrate was recorded as the in vitro disintegration time. It was performed in triplicate

***In vitro* Dissolution Studies**

The *in vitro* dissolution study was carried out in 500 ml pH 6.8 phosphate buffer using (USP) XIV paddle apparatus II at 37^0±0.5°C and at 50 rpm. Each square cut film sample (dimension: 2 cm x 2 cm) was submerged into the dissolution media and appropriate aliquots were withdrawn at 0.5, 1, 1.5, 2, 3, 4, 5 and 10 minute time intervals and again replaced with same volume of dissolution media. The samples were filtered through whatman filter paper for all the batches and analyzed spectrophotometrically at 238 nm (Model UV-1800 UV-Visible spectrophotometer, Shimadzu, Japan).Sink conditions were maintained throughout the experiment. The dissolution test was performed in triplicate for each batch.[6]

Morphology study of film

Morphology of the prepared films was observed under a Scanning Electron Microscope at 1000x by Scanning Electron Microscope.[7]

RESULTS AND DISCUSSION

Table 4: Evaluation parameter of the films prepared using pullulan:

Batch Code	Appearance	Folding endurance	Disintegration Time(sec)	Film Thickness (mm)
P1	Transparent	17±1.0	21±1.25	0.021±0.0015
P2	Transparent	25±1.73	25±1.52	0.029±0.001
P3	Transparent	18±2.0	26±3.0	0.032±0.015

*Standard deviation, mean n =3

Table 5: Evaluation parameters of trial batches with HPMC E grades

Trial code	Appearance	Folding endurance	Disintegration Time (sec)	Thickness (mm) : S.D
$H5_a$	Transparent	32.33±1.52	31±1.98	0.022±0.002
$H5_b$	Transparent	37.66±0.577	45±1.48	0.025±0.006
$H5_c$	Transparent	62.33±0.577	59±3.21	0.023±0.001
$H6_a$	Transparent	42±1.10	28±0.56	0.020±0.0005

$H6_b$	Transparent	49±0.98	30±0.22	0.021±0.002
$H6_c$	Transparent	50±1.23	38±0.86	0.024±0.004
$H15_a$	Transparent	31.66±0.577	40±1.87	0.024±0.002
$H15_b$	Transparent	64.33±0.577	60±1.82	0.024±0.002
$H15_c$	Transparent	61.33±2.08	65±3.22	0.025±0.002

*Standard deviation, mean n =3

Drug excipients compatibility studies by IR Spectroscopy:

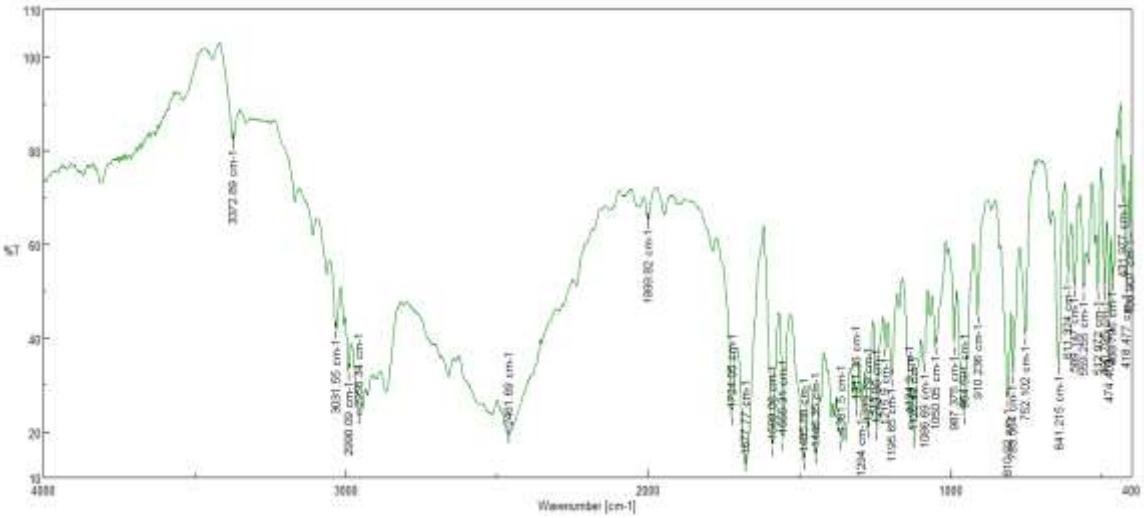

Figure 1: IR spectrum of Buspirone hydrochloride

Table 6: IR data of Buspirone hydrochloride

Sr. No.	Functional group	IR Signals (cm^{-1}) of pure drug
1	C-H Stretching	3031.55
2	C=C Stretching	1589.06
3	C=O Stretching	1724
4	N-H Stretching	3372.89

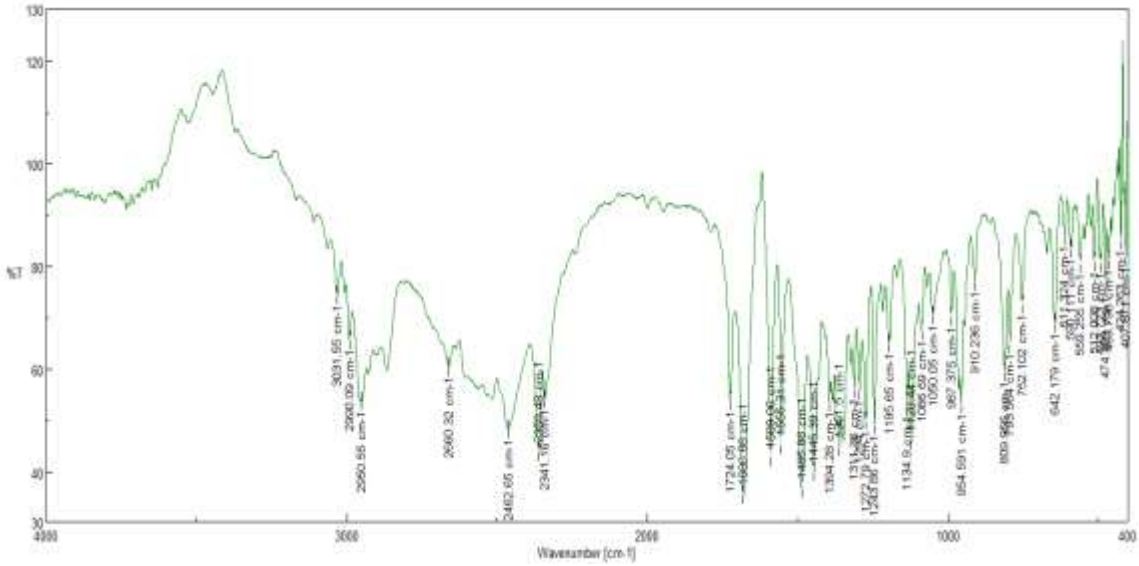

Figure 2: IR spectra of Buspirone Hydrochloride with Pullulan

Table 7: IR data of Buspirone Hydrochloride with Pullulan

Sr. No.	Functional group	IR Signals (cm^{-1}) of formulation
1	C-H Stretching	3031.55
2	C=C Stretching	1589.06
3	C=O Stretching	1724
4	N-H Stretching	3372.89

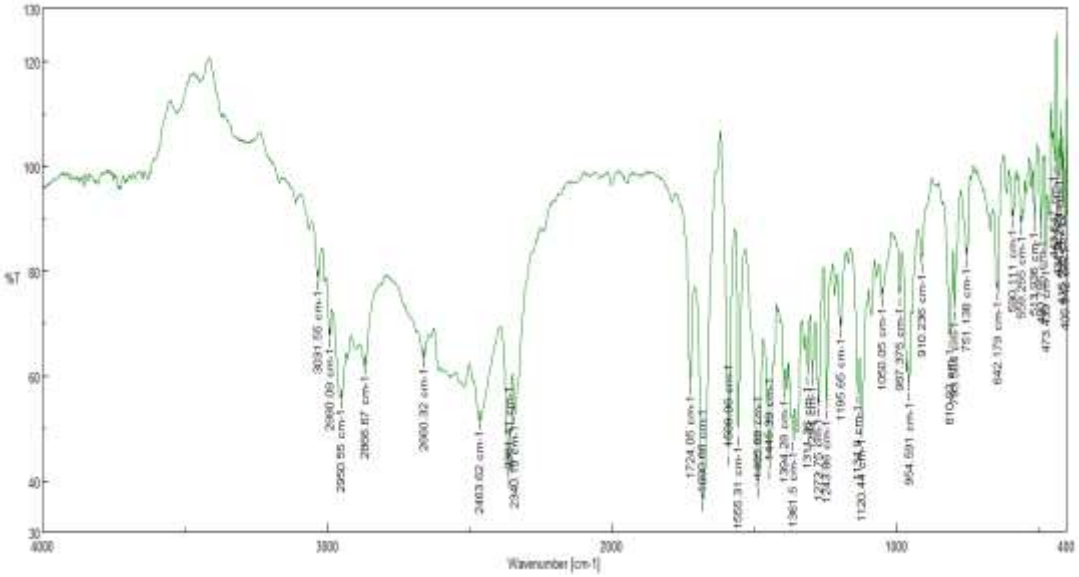

Figure 3 : IR spectra of Buspirone Hydrochloride with HPMC E6

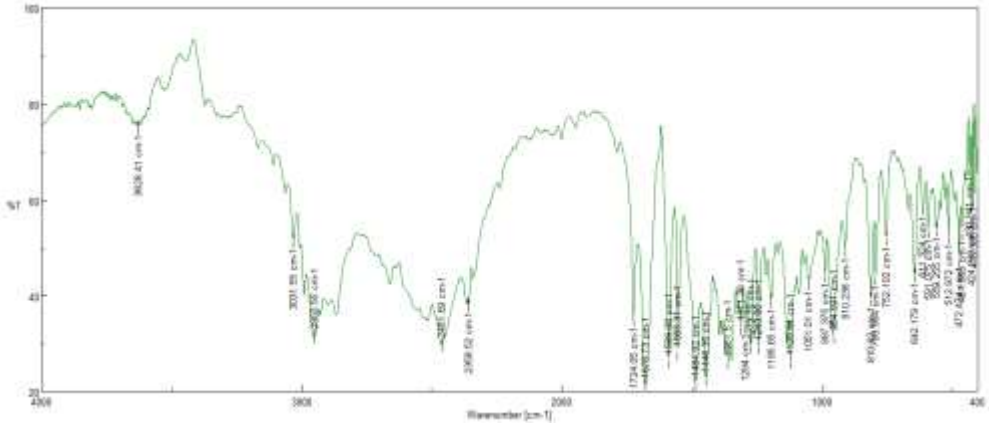

Figure 4: IR spectra of Buspirone Hydrochloride with HPMC E15

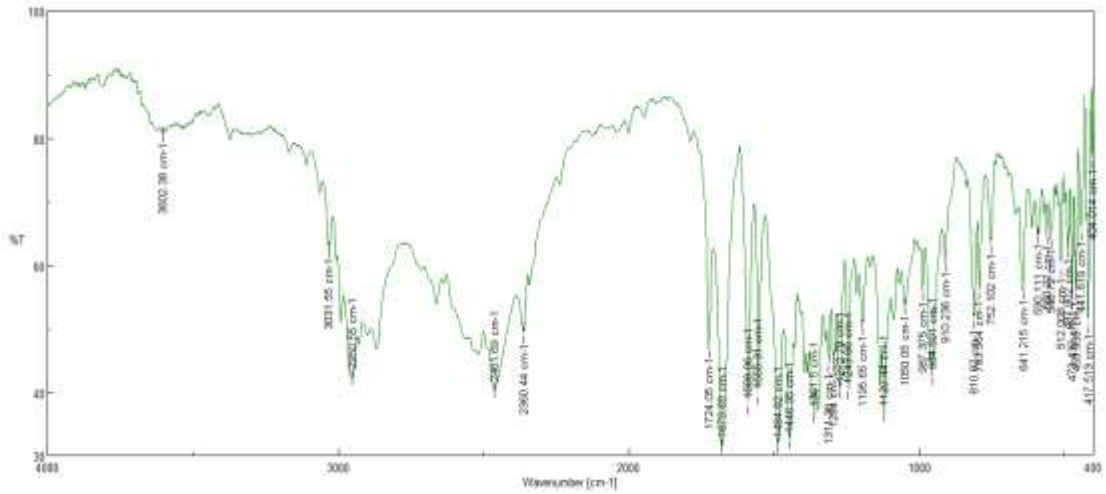

Figure 5: IR spectra of Buspirone Hydrochloride with HPMC E5

Table 8: Evaluation Parameter of Formulation Batches

Batch Code	Tensile strength (gm/cm ^{2})	Disintegration Time (sec)	Folding Endurance	% Drug content	Weight Variation	Film Thickness	pH of film
F1	12.66±0.577	19±1.25	10.33±0.57	97.8	362.23±0.25	0.021±0.0015	6.82±0.05
F2	15.33±0.5	21±1.52	14±1.75	99.2	462.06±0.11	0.029±0.001	6.75±0.03
F3	19±1	24±3.0	14.23±1.15	97.4	562.2±0.346	0.032±0.015	6.85±0.06
F4	9.33±0.5	20±1	9.33±0.577	98	363±1	0.025 ±0.004	6.82±0.05
F5	11±1	22±0.577	11.33±0.5	98.8	462.35±0.40	0.027±0.003	6.78±0.05
F6	12.66±0.577	24±1	12±1	97.2	562.39±0.49	0.029±0.004	6.82±0.06

*Standard deviation, mean n =3

Table 9: Cumulative % Drug release of formulation Batches

Time (Min)	Cumulative % Drug release					
	F1	F2	F3	F4	F5	F6
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
0.5	14.83±0.288	11.66±0.763	12.00±0.5	11.5±0.5	14.23±0.25	13.8±0.98
1	28.83±0.763	34.5±0.5	29.5±0.5	28.83±0.76	30.5±0.7	38.53±0.47
2	40.16±0.288	61.33±0.288	59.36±0.346	58.16±0.76	43.66±0.41	53.5±0.5
3	69.33±0.577	79.33±0.288	80.83±0.5	72.5±0.435	75.03±0.25	74.46±0.41
5	95.83±0.763	97.16±0.288	96.33±0.288	94.16±0.28	95.06±0.11	96.2±1.04

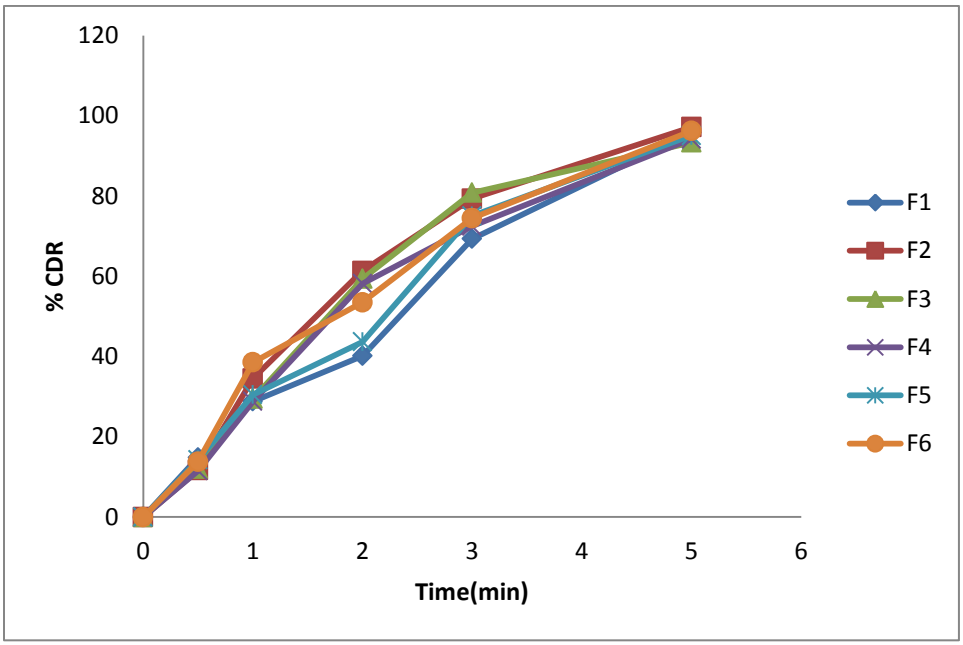

Figure 6: Cumulative % Drug release of formulation Batches

DISCUSSION:

Fast Dissolving Oral films are intended for the application in the oral cavity and they are an innovative and promising dosage form especially for use in paediatrics and geriatrics. On the Indian market no licensed Fast Dissolving Film drug product is available yet.

Buspirone hydrochloride was selected as the active drug as it has very high solubility and it is indicated in to anxiety where an immediate relief is always needed. Moreover mouth dissolving Film dosage form is very convenient for geriatric patient and those who have difficulty in swallowing tablets or in situations where access to water is not possible.

Drug-free films were prepared according to the literature starting with a pre evaluation of different film formers such as, Pullulan, Maltodextrin and HPMC E series. Among them Pullulan and HPMC E series polymers were evaluated for further use in drug-loaded oral films. The characterization of drug and drug polymer interaction were carried. The oral films prepared using both polymers Pullulan and HPMC E series were evaluated with regard to their film forming capacity, disintegration time, mechanical properties and % Drug release. Both the polymers have better film forming capacity but pullulan has faster disintegration than HPMC E series. Low viscosity HPMC E series polymers and pullulan are evaluated gives good mechanical properties with better drug release. Pullulan film evaluated with use of different plasticizer like glycerine, PEG 400. Glycerine gives fast dissolving film with good mechanical properties.

Optimized film of pullulan was also evaluated for morphology checked by Scanning Electron Microscopy. Increase in the levels of Glycerin causes an increase in the Folding Endurance while

Pullulan had a negative effect. A plasticizer has a negative effect on the Drug Release. % Drug Release of the film increased with decrease in levels of both polymer and plasticizer. Stability study of optimized Fast Dissolving Film of Buspirone hydrochloride was revealed for 3 month which shows no significant difference.

CONCLUSION

The Novel dosage form Fast dissolving Film for oral cavity was formulated and evaluated. This study revealed, successful formulation of Fast Dissolving oral film. The produced Fast dissolving oral film showed highest drug release and average folding endurance. The high % drug release of the film in phosphate buffer pH 6.8 at 5 min indicated that these films can be real alternative product like tablets and capsules. This could be helpful for the treatment of diseases where quick bioavailability of the drug is desired for example: acute and chronic asthma.

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