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FORMULATION, DEVELOPMENT AND EVALUATION OF ORAL FAST DISSOLVING FILMS OF PRUCALOPRIDE

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- **Abstract**

Oral fast dissolving films (OFDF) dissolves rapidly along with drug in mouth and majority of the drug is absorbed through Buccal / oral mucosa in to systemic circulation avoiding first pass metabolism. The aim of present investigation was to Formulate & Evaluate oral fast dissolving films (OFDF)of Prucalopride (Prokinetic/Enterokinetic agent), which is used on Functional or Chronic constipation. Oral films were prepared by Solvent casting method using HPMC E15 as a film forming agent and PEG 400 was used as plasticizers. Citric acid as salivary stimulating agent and Aspartame as sweetening agent is also used. The films were evaluated with disintegration time, Folding endurance, Tensile Strength, Thickness, Surface pH, Moisture content Drug content uniformity and *In-vitro* dissolution studies. All formulations showed good mechanical properties and *in vitro* drug release. The optimized F5 Formulation batch Exhibited drug release of 93.44% in 15 minutes with 27 sec disintegration time which was significantly better as compared with other batches. Drug loaded films of F5 batch; stability optimized under 40°C/75% RH conditions.

- **Keywords**

Drug-Prucalopride, HPMC E15, PEG-400, Citric acid, Aspartame, S o l v e n t

- **Introduction**

Oral fast dissolving drug-delivery systems (OFD-DDS) were developed in the late 1970's to overcome the problem of difficulty in swallowing of solid dosage forms.These systems consist of oral dispersible tablets (ODT) andoral dissolving film (ODF) that are disintegrate as well as dissolve quickly in the oral cavity.Oral dissolving film (ODF) for oral administration was a novel approach, for the patients who experience difficulties in swallowing tablets or capsules. Geriatric, pediatric and dysphasic patients

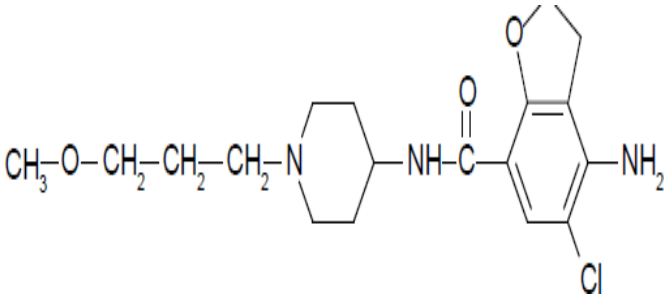
associated with many medical conditions face a problem of difficulty in swallowing the solid dosage forms. Hence, without swallowing and without water oral strips and oral films which rapidly dissolves under the tongue or buccal cavity, could also improve the dissolution of poorly soluble drug.**(Ali MS et al., 2016)**

The oral delivery is currently the gold standard in the pharmaceutical industry, where it is regarded as the most convenient, safest and economical route of drug delivery.

When administration is considered, the oral cavity can be cited as one of the best sites for the delivery of drugs. Mucosal and Trans mucosal (local effect and systemic effect, respectively) drug administration can be achieved through this route. The effect of the former is such that a site- specific release of the drug on the mucosa is achieved, and in the latter, the drug reaches the systemic circulation by the way of mucosal barrier and gets absorbed. The vascularization is high in oral mucosa, and enzymatic activity is minimal as that of nasal, intestinal, and rectal mucosa. On account of irritation and impairment, the oral mucosa is less sensitive than the nasal epithelium. In trans mucosal drug administration, the sublingual and buccal mucosa work as absorption sites that has two curative goals. The sublingual process is made use of in the treatment of acute disorders. Since it has a high permeability across the mucosa, it is generally administered for the delivery of drugs. When a continuous release of the active substance becomes necessary as in the case of chronic disorders; the buccal process is generally employed. However, the sublingual process has pitfalls. The activity of the tongue hampers the contact of the dosage form with the mucosa, further worsened by the surface being incessantly washed by saliva.**(Gandhi et al., 1994).** Buccal process is more suitable for the placement of control release system which the patient also receives well. When compared to sublingual, buccal mucosa is flush and has surface which is immovable.

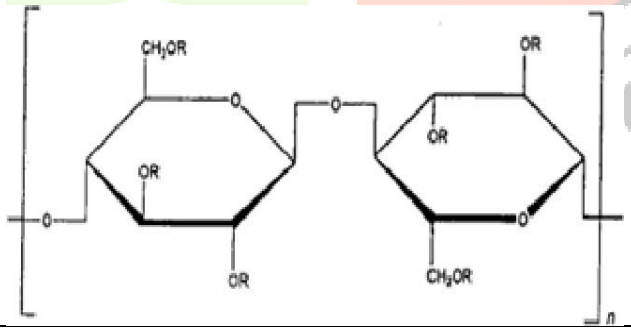
- **DRUG AND EXCIPIENT PROFILE**

- **Drug profile (Prucalopride)**

Structure	
IUPAC name	4-amino-5-chloro-2,3-dihydro-N-[1-(3-methoxypropyl)-4-piperidinyl]-7-benzofurancarboxamide butanedioate
Molecular formula	C18H26ClN3O3
Molecular weight	367.87g/mol
Category	Prokinetic / Enterokinetic Agent
Appearance	Prucalopride is a white to almost white powder
BCS class	Class I
Solubility	It issoluble in water and Ethanol
Melting point	198^0C
Partition coefficient	4.94
Bioavailability	>90%.
Pka	6.1
Absorption	Prucalopride is rapidly absorbed; after a single oral dose of 2 mg, Cmax was attained in 2-3 hours. The absolute oral bioavailability is >90%. Concomitant intake of food does not influence the oral bioavailability of prucalopride.
Mechanism of action	*In vitro* studies of prucalopride showed its high affinity for human and animal 5-HT4 receptors at concentrations that are comparable to the clinical exposure. These responses were blocked by 5-HT4 receptor antagonists. Prucalopride had a low affinity for other 5-HT receptor subtypes. In animal studies ,

	prucalopride had a significant effect on propulsive motor patterns in the colon and stomach.
Half life	*24-30 hrs*
Protein binding	*The plasma protein binding of prucalopride is about 30%.*

- **HPMC-E15**

Description	Hypromellose is odorless and tasteless, white or creamy white colored fibrous or granular powder.
Sturcture	
Synonym	HPMC, Methocel, Pharmacoat.
Non proprietary names	B.P Hypromellose, U.S.P: Hypromellose, JP: Hydroxypropyl methylcellulose.
Chemical name	Cellulose, 2- Hydroxypropyl methyl ether.
Molecular weight	12,000-15, 00,000 dalton.
Category	Coating agent, film former, rate controlling polymers for sustained release drug delivery system, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.
Solubility	in cold water, insoluble in chloroform, ethanol and ether but soluble in mixtures of ethanol and dichloromethane and mixtures of methanol and chloromethane.

- **Polyethylene glycol400**

Description	Polyethylene glycol is being an addition polymer of ethylene oxide and water.
Synonym	Carbowax; Carbowax Sentry; Lipoxol; PEG; polyoxyethylene glycol.
Chemical name	A-Hydro-o-hydroxypoly (oxy-1,2-ethanediyl)
Molecular weight	4400–4800
Category	Ointment base, plasticizer, solvent, suppository base, tablet and capsule lubricant.
Stability	Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid.
Incompatibilities	All grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation

- **MATERIALS AND METHODS**

1. **List of chemicals**

Name	Supplier Name
Drug.	
Prucalopride	Cipla Pvt. Ltd., Mumbai, India
Polymer.	
HPMC E 15	Rankem Chemical Pvt. Ltd.
Chemicals.	
PEG- 400	Loba Chemical Pvt. Ltd.

2. List of equipment's

Instrument Name	Model No.
Digital Weighing Balance	AUX 120, Shimadzu, Japan.
Magnetic Stirrer	Remi, Mumbai, India
Orbital Shaking Incubator	CIS-24, Remi Instruments Ltd., India.
Ultraviolet Spectrophotometer	Shimadzu 1700 Japan.
Differential Scanning Calorimeter	DSC 822c, Mettler Toledo Pvt. Ltd., Switzerland.
Infra-Red Spectrophotometer	FTIR-8400S, Shimadzu, Japan.
Ultra Centrifuge	Bachman Coulter, Saint Lucia, USA.
pH Meter	µpH system 362, Systronics Ltd., India.
Stability Chamber	CHM-10S, Remi, India.
Ultra Sonicator	Lab Hosp, Mumbai.
Pellet press	Kimaya Engineers, India
Dissolution test apparatus	Electrolab, Mumbai

- **Formulation of films(Solvent Casting Method)**

Fast dissolving filmsof Prucalopride were prepared by solvent casting technique.

⇩

Drug is dissolved in the 10ml distilled water using magnetic stirrer

⇩

Polymer and Other excipients are dissolved in another 10ml distilled water

⇩

Drug solution is added to the polymer solution and mix together with the help of magnetic Stirrer

⇩

The whole solution was poured into Petri plate.

⇩

The Plate containing polymeric solution of drug was kept 12 hours at room temperature for drying.

⇩

After Drying of films, films placed in the Desiccator

- **Method of preparation of oral films**
- **Composition of oral films.**

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F 9
1.	**Prucalopride**(mg/ film)	1	1	1	1	1	1	1	1	1
2.	**HPMCE15**(%)	2	2	2	2.5	2.5	2.5	3	3	3
3.	**PEG-400**(%)	4	6	8	4	6	8	4	6	8
4.	**Citric acid**(%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0. 5
5.	**Aspartame**(%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0. 5
6.	**Flavor**(%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0. 2
7.	**Water** (Up to ml)	10	10	10	10	10	10	10	10	1 0

- **Evaluation of buccal films**
- **Surface texture and physical appearance**

Physical appearance and Surface texture of patches prepared using different concentration of HPMC.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. The results are shown in Table 7.7**.**

- **Weight uniformity**

The assessment of weight was done in 3 different randomly selected patches from each formulation. Patches were directly weighed on a digital balance. Drug loaded film was tested for uniformity of weight and the results are given in the table: 7.8. The weight of all the prepared batches was found to quite uniform. Standard deviation of all the film ranged between 126 and 142.

- **Thickness**

The assessment of patch thickness was done in 3 different randomly selected patches from each formulation. Patch thickness was measured at 5 different randomly selected spots on patches using a screw gauge.

- **Surface pH**

  A combined glass electrode was used for this purpose. The patches were allowed toswell by keeping them in contact with 1 ml of distilled water (pH 6.8±0.1) for 2 hrs. at room temperature, and pH was noted down by bringing the electrode in contact with the surface of\ the patch, allowing it to equilibrate for 1 min. The surface pH of the patches was determined in order to investigate the possibility of any side effects in the oral cavity. As acidic oral alkaline pH is bound to cause irritation to the buccal mucosa, hence attempt was made to keep the surface pH of the patches close to the neutral pH

- **Folding endurance**

  Folding endurance of patches was determined by repeatedly folding one patch at the someplace till it broke or folded up to 300 times without breaking. Folding endurance of the 2x2cm films was determined by repeatedly folding one film at the

Same place till it broke or folded upto 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on two individual films of each formulation batches.

- **Percent moisture absorb**

The weighed patches were kept in desiccators at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs, the film were reweighed and determine the percentage moisture uptake from the below mentioned formula.

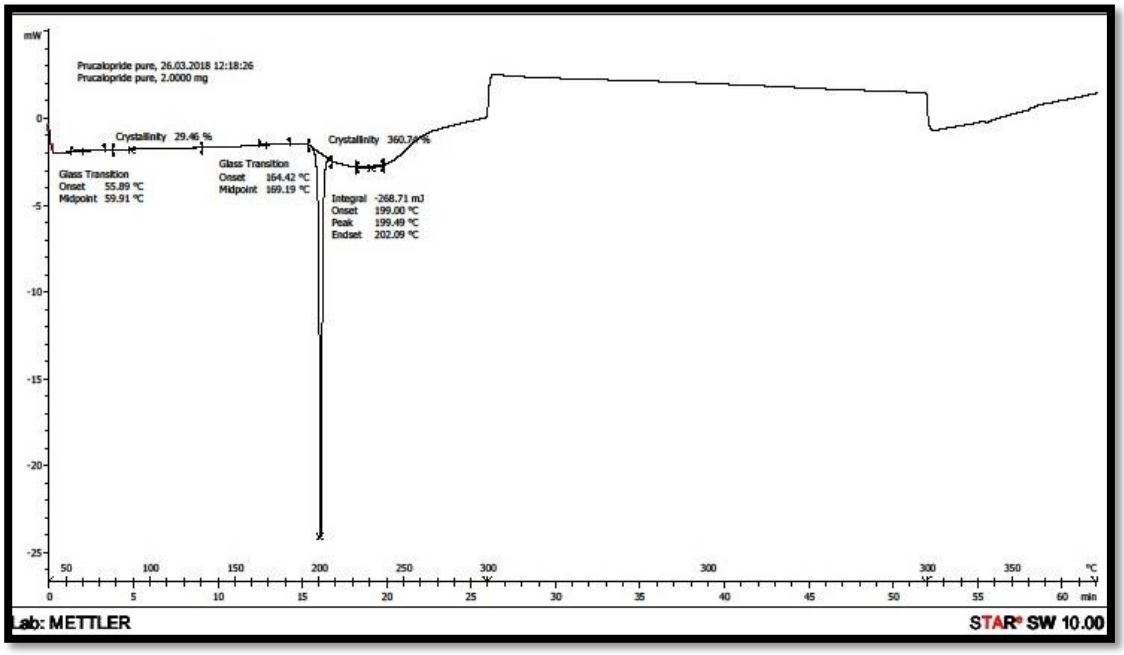
- **RESULTS AND DISCUSSION**

- **Differential scanning calorimetry (DSC)**

DSC thermo gram of pure drug Prucalopride.

Thermal properties of the drug was evaluated by means of DSC.The DSC thermogram of Prucalopride is shown in Fig. No.7.1.The onset temperature was reported in the graph. The melting point of Prucalopride was 197-199°C and DSC thermogram of Prucaloprideshows endothermic melting peak at 199°C.

Melting point was determined by using differential scanning calorimetry. Thermogram for the drug was obtained using DSC (Mettler DSC 1 star system, Mettler-Toledo, Switzerland). The drug sealed in perforated aluminum pan and heated at a constant rate of 10^{o}C/min over the temperature ranges of 30-300^{o}C



- **Infrared Spectroscopy**

- **Concentration and absorbance of Prucalopride in water**

Conc. (µg/ml)	Absorbance (nm)
0	0
2	0.204
4	0.396
6	0.585
8	0.816
10	0.958

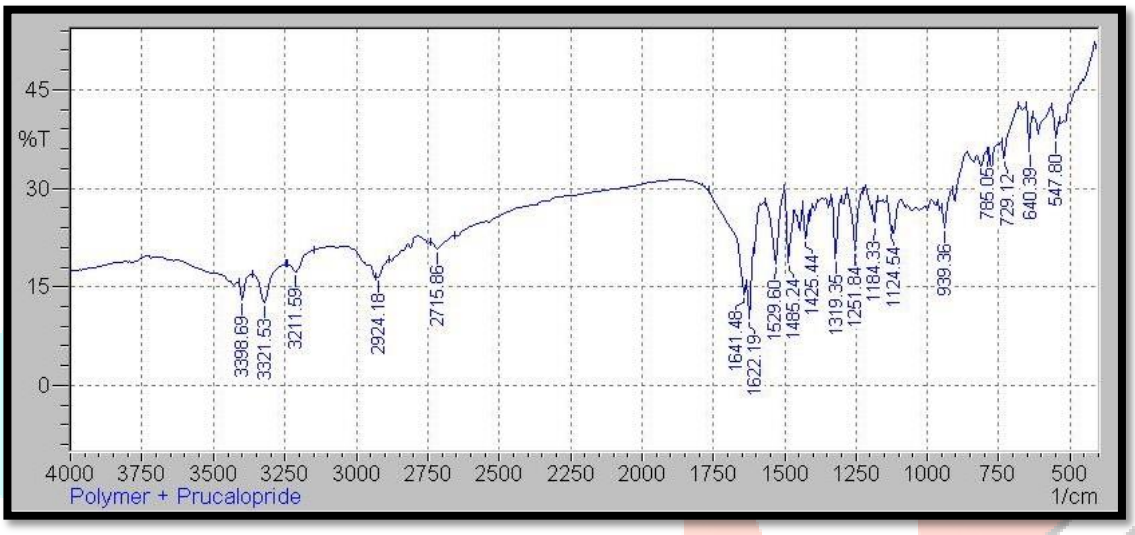
- **Standard calibration curve of Prucalopride in pH 6.8 buffer**

Solubility of Prucalopride

The saturation solubility of pure drug Prucalopride was determined in differentsolvents like as water , buffer pH 6.8 and ethanol .The drug weighed accuratelyin

- **Compatibility Study**
- **Fourier Transform Infrared (FTIR) Spectroscopy**

Drug excipient interaction study



- **IR Ranges of Drug and Polymer**

Drug peak	HPMC	Interaction
2924	1760	No interaction
3398	1690	
1622	1550	
1641	1350	

- **IR ranges of Drug excipient (physical mixture)**

Drug peaks (cm^{-1})	Drug+Polymer peaks (cm^{-1})	Interaction
3398, 3321, 3211, 2926, 2715, 1641, 1622, 1529, 1425, 1319, 1184, 937, 640, 547 .	3398, 3321, 3211, 2924, 2715, 1641, 1622, 1529, 1425, 1319, 1184, 939, 640, 547 .	No interaction

Peaks shown by FTIR spectra in Prucalopride drug and the physical mixture of drug and polymers. The characteristic peaks of the drug are also present in the spectra of allthe drug-polymer combinations. Thus, we can conclude that there was no any kind ofinteraction was found between drug and polymer. Hence it was considered as suitable of polymer for the formulations.

- **Physical appearance and surface texture**

Physical appearance and Surface texture of patches prepared using different concentration of HPMC.

- **Physical appearance and surface texture of films**

Formulation code	Appearace	Surface texture
F1	Transparent White	Smooth
F2	Transparent White	Smooth
F3	Transparent White	Smooth
F4	Transparent White	Smooth

F5	Transparent White	Smooth
F6	Transparent White	Smooth
F7	Transparent White	Smooth
F8	Transparent White	Smooth
F9	Transparent White	Smooth

7.0 Weight uniformity

Drug loaded film was tested for uniformity of weight and the results are given in the table: 9. the weight of all the prepared batches was found to quite uniform. Standard deviation of all the film ranged between 126 and 142. The change in the concentrationof polymers and plasticizer did not show the difference in the weight of film.

Table no7.8: Weight uniformity of buccal films

Formulation code	Weight of films (mg)
F1	129 ± 2
F2	136 ± 2
F3	133 ± 3
F4	142 ± 2
F5	131 ± 3
F6	136 ± 2
F7	140 ± 1
F8	139 ±2
F9	127 ±2

7.1 Thickness uniformity

The thicknesses of drug-loaded film were measured with the help of Vernier Caliper.At four sides and one in center of films. The mean values are shown in the table.

- **Thickness of films**

Formulation code	Thickness of Buccal films (mm)
F1	0.12
F2	0.13
F3	0.13
F4	0.14
F5	0.16
F6	0.15
F7	0.17
F8	0.16
F9	0.19

- **Surface pH:**

The surface pH of drug loaded film were measured with the help of the electronic pHmeter.

- **Surface pH of prepared films**

Formulation code	pH of Films
F1	**6.7**
F2	**6.5**
F3	**6.6**
F4	**6.4**
F5	**6.8**
F6	**6.7**
F7	**7.0**
F8	**6.8**
F9	**6.4**

- **Folding endurance**

Folding endurance of the 2x2cm films was determined by repeatedly folding one film at the same place till it broke or folded upto 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on two individual films of each formulation batches.

- **Folding endurance of buccal films**

Formulation code	Folding endurance
F1	232
F2	246
F3	265
F4	249
F5	282
F6	277
F7	254
F8	278
F9	289

- **Percentage moisture absorb**

The weighed patches were kept in desiccators at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs, the film were reweighed and determine the percentage moisture uptake from the below mentioned formula.

- **Percentage moisture absorb of films**

Formulation code	Moisture Absorbed in %
F1	9.79
F2	10.52
F3	8.90
F4	15.47
F5	12.08
F6	10.52
F7	13.58
F8	10.19
F9	9.9

- **Disintegration time**

A glass petri dish (6.5cm diameter) was filled with 10ml of water and the film was carefully placed in the petri plate which containing water. The set up was left undisturbed. The time which waste film is completely disintegrate means begins to break down.

- **Disintegration time of prepared films**

Formulation code	Disintegration time (sec)
F1	29
F2	27
F3	31
F4	28
F5	27
F6	30
F7	28
F8	29
F9	28

- **Drug content uniformity**

The content uniformity test is commonly employed for unit dosage forms. In order to make sure about the uniform dispersion of drug in film, the drug content was carried out. The drug content was analyzed at 227 nm by using suitable blank. All the formulations showed more than 80% of the drug loading indicating much of the drug is not lost. The results were expressed and reported in table7.14. The results indicatedthat the drug was uniformly dispersed.

- **Drug present in the prepared films**

Formulation code	Drug present (%)
F1	88.5
F2	79.2
F3	87
F4	83.3
F5	92.10
F6	91.5
F7	90.11
F8	87.5
F9	89.5

- ***In-vitro* drug release study**

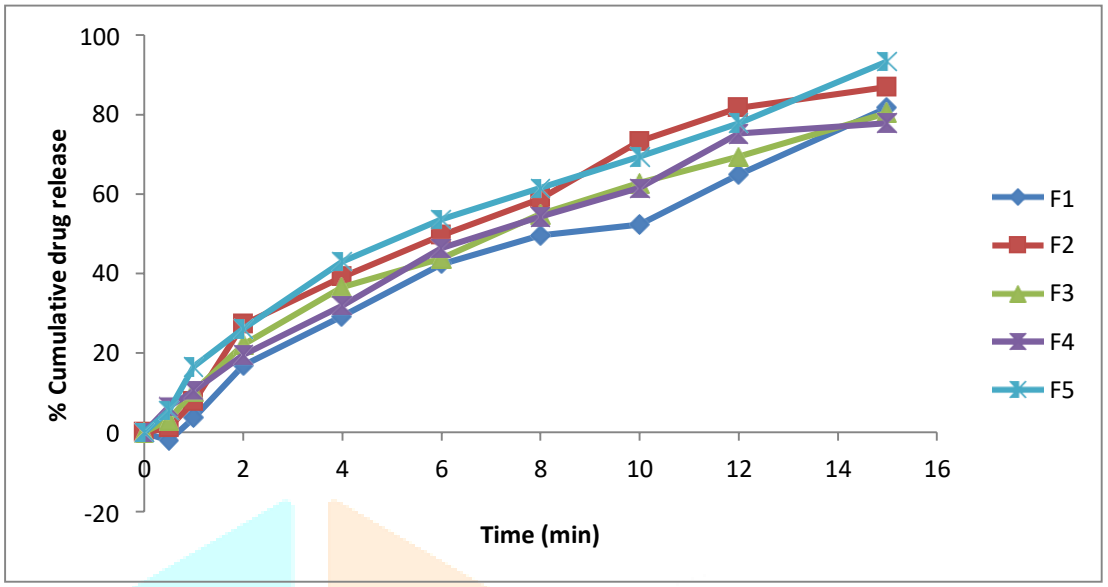
The veggo VDA-6D USP eight station dissolution apparatus was used throughout the study. The dissolution study was performed by using basket type setting where, one film of each batches was fixed inside the basket. The dissolution media consist of 500ml of 6.8 Buffer. The release study was performed rotation speed of 50 rpm and a temperature of 37°C ± 1°C was maintained throughout the experiment. The release study was carried out for 15 Minute. After 0.5, 1, 2, 4, 6, 8, 12 &15min interval 5ml of sample was withdrawn and the same was replaced back with buffer pH6.8 solution.Each withdrawn sample was filtered, diluted suitably and then analyzed spectrophotometrically at 227nm. The experiments were performed in triplicate, and average values were reported.

- **In-vitro drug release of oral films**

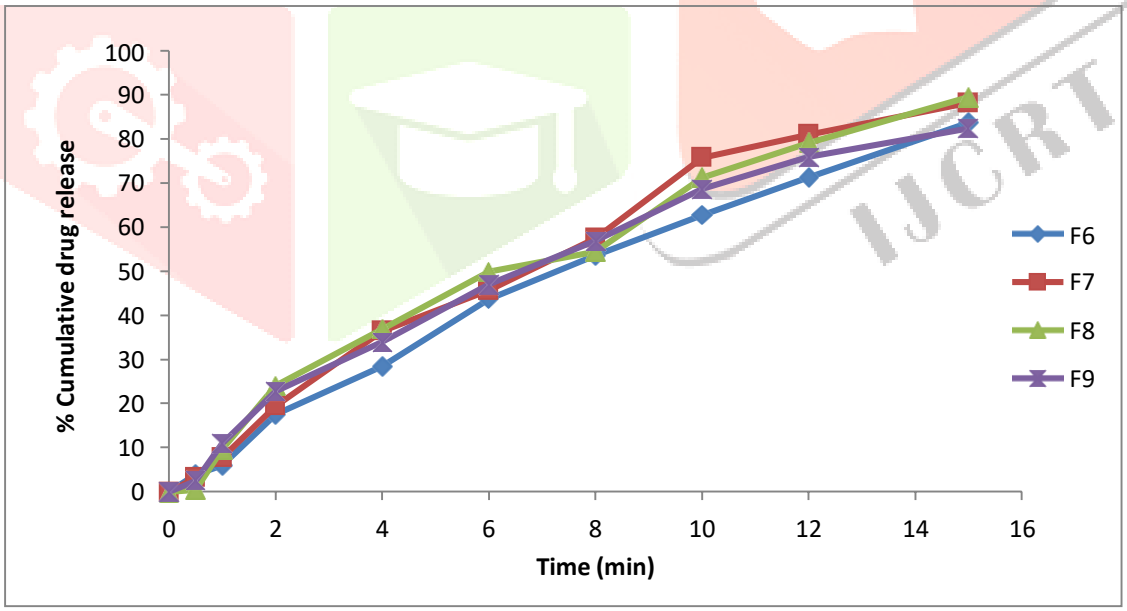
Time(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	-2	1.25	3.15	6.50	5.50	3.95	3.20	0.50	2.55
1	3.78	7.74	10.33	10.51	16.56	6.04	7.73	9.66	10.98
2	16.85	27.28	22.12	19.52	26.07	17.53	19.49	24.66	22.77
4	29.32	39.17	36.52	31.95	43.05	28.51	36.49	36.95	33.93
6	42.43	49.67	43.80	46.36	53.61	43.73	45.75	49.94	47.03
8	49.70	58.87	54.91	54.29	61.51	53.62	57.53	54.48	56.90
10	52.37	73.25	62.82	61.51	69.30	62.80	75.83	71.36	68.68
12	64.87	81.75	69.42	75.26	77.86	71.36	81.10	79.16	75.91
15	81.75	86.95	80.45	77.86	93.44	83.70	88.25	89.55	82.40

- **In-vitro drug release after 15 min.**

Formulation code	In vitro % drug release after 15min
F1	81.75
F2	86.95
F3	80.45
F4	77.86
F5	93.44
F6	83.70
F7	88.25
F8	89.55
F9	82.40



Graphical representation of *In-vitro* release study of formulationbatches of F1,F2,F3,F4 and F5



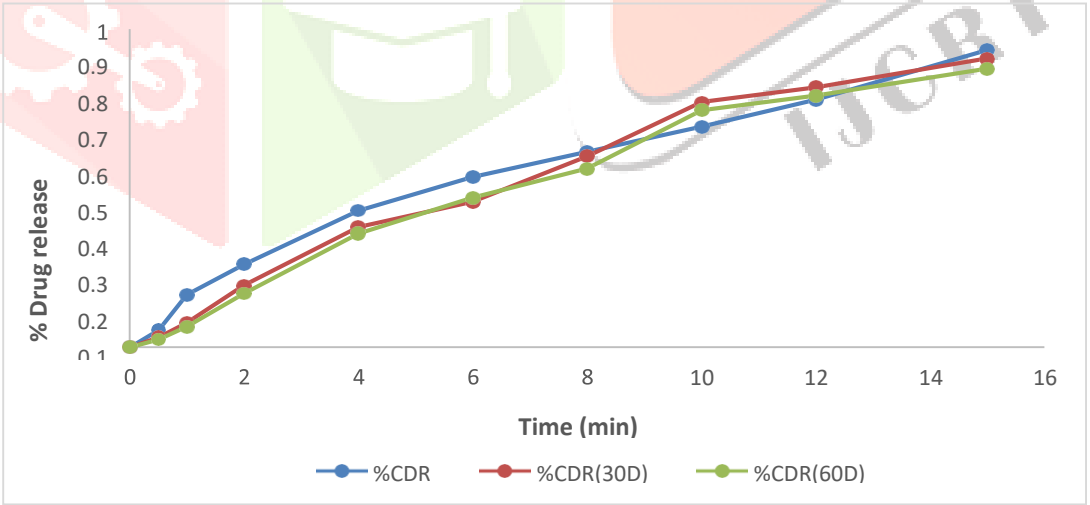
Graphical representation of *In-vitro* drug release study of different formulation of F6,F7,F8 and F9.

- **Stability study**

The optimized formulation batch F5 was evaluated at the time interval of 60 days for the all the parameters like Appearance, weight, thickness, % drug content and % drug release. The observations of stability studies of optimized formulation batch F5are shown in given table did not show any significant change in these parameters after stability studies. This confirms the stored film formulation were stable for the storage period.

- **Stability study**

Duration	**Apperance**	**Thickness**	**Drug content**	**Drug release**
0 days	Tranparent White	0.16mm	92.10%	93.44%
30days (40°C/75% RH)	Tranparent White	0.16mm	91.67%	90.84%
60 days (40°C/75% RH)	Tranparent White	0.16mm	90.37%	87.60%



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