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A COMPARATIVE STUDY ON DIFFERENT POLYMERS FOR THE PREPARATION OF FAST DISSOLVING ORAL FILMS OF LOPERAMIDE HYDROCHLORIDE

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ABSTRACT

In the present work, aimed to a comparative study on different polymers for the preparation of fast dissolving oral films of loperamide hydrochloride as an anti-diarrhoeal drug using different ratios of polymers, Hydroxypropyl methylcellulose K 100 M, sodium carboxy methyl cellulose, poly vinyl alcohol cold as film forming agents. The film was prepared by solvent casting technique using propylene glycol as a plasticizer, sodium saccharin as a sweetener. The study examines about the effect of polymers ratio on physicochemical properties and drug release potential of films. All the films formulations (F1-F8) were evaluated for their thickness, weight variations, tensile strength, thickness, folding endurance, surface pH, in -vitro disintegration, drug content, In-Vitro drug release and stability study. The formulation, (F7) consisting of 130 mg of HPMC K 100 M, 150 mg of sodium carboxy methyl cellulose and 50 mg of poly vinyl alcohol cold was found to be best among all other formulations in the form of fast dissolving film based on the in vitro evaluation studies. The (F7) showed optimum disintegration time 50.33 ± 0.57 sec and percentage drug release 96.84± 0.79 %.

KEYWORD: Loperamide hydrochloride, HPMC K 100 M, SCMC, PVA cold, Solvent casting method.

INTRODUCTION

Development of a drug is a process that brings a new pharmaceutical drug into the market once a lead compound has been identified through drug discovery process.[1] Research and development of the drugs lead to the faster growth in the pharmaceutical industry.[2] Many

years are taken for the travel of the drug from the research to the consumer or patient through the drug development process. For the success of an industry, they are mainly concentrating on the research and development of a new drug and the development of the different dosage form of the currently existing drugs. Now a day variety of drugs is available in the market in different dosage form based on the route of administration Research and development in the oral drug delivery systems show the transition of the dosage form from simple conventional tablet or capsule to modified release tablets or capsules to oral disintegrating tablets and fast dissolving oral films.

Fast dissolving oral film is relatively a new dosage form and it is also termed as a thin film drug delivery system or oral drug strip. Through this drug delivery system, the absorption of the drug mainly occurs via absorption in the mouth and/or via the small intestine. The fast dissolving oral films are prepared by using hydrophilic polymers which are easily disintegrated within the oral cavity while it comes in contact with the saliva. No need of water or other liquid for the administration of this type of dosage form is one of the advantages over the conventional dosage forms. After the approval from the regulatory authorities like FDA, currently many oral films are available in the market. The user can place the strip orally and as the strip dissolves within the mouth cavity, the medication enters into the systemic circulation directly through the sublingual route for its pharmacological action or local action.

The digestive system is one of the important systems to overall health. Diarrhea is a common digestive complaint. Diarrhea is a condition of having at least three loose or liquid bowel movements each day. The condition existing for a prolonged period of time. This condition leads to fluid and electrolyte loss from the body.

Loperamide hydrochloride is an antimotility or widely used to treat sudden short term or chronic diarrhea. It is an opiate analog with major peripheral μ opioid and additional weak anticholinergic property. Sometimes the use of this anti motility drug makes short-term constipation. Loperamide hydrochloride is little absorbed from the small intestine because of its poor solubility in the water.

Opioid receptors are mainly present on the neurons in the CNS and in peripheral tissues. Morphine and other opioids show their pharmacological action by interacting with these specific receptors. Radioligand binding studies divided the opioid receptors into 3 types, they

are mue, kappa, delta which has been cloned, mapped and studied with modern techniques. Each type of this receptors has a specific pharmacological profile and pattern of anatomical distribution in the brain, spinal cord and peripheral tissues (mainly gut, blood vessels, heart, lungs and immune cells). Among these 3 types of the receptors, loperamide hydrochloride as high-affinity towards μ opioid receptors. The direct interaction with the calmodulin may be responsible for the antidiarrhoeal action. Entry into the brain is negligible. CNS effects are rare. CNS effects may occur when the dose is higher than the recommended dose. The loperamide hydrochloride has the duration of action 12 hrs. Opioid receptors are present in the myenteric plexus of the large intestine; while the drug molecule bind with these receptors in the myenteric plexuses, decrease its activity thereby decrease the motility of the circular and longitudinal smooth muscles of the intestinal wall.

In this research work, a comparative study on different polymers for the preparation of fast dissolving oral film of loperamide hydrochloride has been carried out. Loperamide hydrochloride is an antidiarrhoeal drug and the study was carried out by using hydrophilic polymers such as hydroxyl propyl methyl cellulose K 100 M (HPMC K100 M), sodium carboxy methyl cellulose (SCMC), polyvinyl alcohol cold (PVA Cold). The design of the study is 2^3 factorial designs.

MATERIALS AND METHODS

Loperamide hydrochloride was a gift sample from Gifted from Caplin Point Laboratories Ltd. Hydroxy propyl methyl cellulose K100 M, Sodium carboxy methyl cellulose, Poly vinyl alcohol cold, Sodium saccharin, Citric acid, Orange oil Propylene glycol, Sunset yellow and ethanol purchased from Burgoyne Burbidges & Co, Mumbai, India.

METHOD OF PREPARATION OF FAST DISSOLVING ORAL FILM OF LOPERAMIDE HYDROCHLORIDE

SOLVENT CASTING METHOD[3,4,5]

Fast dissolving oral film of loperamide hydrochloride was prepared by solvent casting method. All batches of films were developed as shown in the table: 1.The polymeric solutions were prepared separately by using 3 different types of polymers namely hydroxyl propyl methyl cellulose K 100 M, sodium carboxy methyl cellulose, poly vinyl alcohol cold. The optimized amount of selected polymers were dissolved in the 10 ml of water and stirred continuously for 1 hour by using magnetic or mechanic stirrer.

Optimized amount of sweetener, plasticizer, saliva stimulating agent is dissolved in 5 ml of water. Sunset yellow used as a coloring agent, it is dissolved in 5 ml of water in another beaker. Both 5 ml solutions are mixed together and add to the above prepared polymeric solution. The quantity of drug was calculated as per the area of petridish so that each film 1x1cm^2 area contained an Optimized amount of drug. Loperamide hydrochloride dissolved in ethanol water mixture in 1:1 proportion (2.5 ml water and 2.5 ml ethanol). The drug solution was added to the polymeric mixture and it was stirred for 1 hour using magnetic stirrer. The casting solution kept in undisturbed condition till the entrapped air bubbles were removed. This solution was cast in a glass petriplate (Figure 5) having 51.5038 cm^2 surface area and was dried at room temperature (25^0-30^{0}C, 45%RH) as well as at increased temperature. The film took approximately 48 hours to dry at controlled room temperature. The dried films are cut into 1 cm^2 area and they are subjected to further evaluations of the product.

The amount of drug incorporated into the polymeric mixtures[6]

Area of the circle = πr^2

Area of the petriplate = π x $(4.05)^2$

= 3.14 x $(4.05)^2$

= 51.5038 cm^2

51.5038 cm^2 area contain 51.5038 mg of drug

51.5038 cm^2 area = 51.5038 x 2

= 103.007 mg drug

1cm^2 area contain = 2 mg drug

Design of Experiment: **2^3 Factorial Designs[7]**

In statistics, a factorial experiment is an experiment, whose design consists of two or more factors, each with discrete possible values or "levels", and whose experimental units take on all possible combination of these levels across all such factors. In this experiment, the design is 2^3 factorial design were two levels ie, high levels and low level and three factors are selected as 3 polymers.

Table no.1: High and low levels of selected polymers.

Polymers	High level (+)	Low level (-)
HPMC K 100 M	200mg	130mg
SCMC	150mg	50mg
PVACold	150mg	50mg

Table no. 2: Factorial design for the Formulae.

Factorial design	Factors		
2^3 Factorial design	HPMC K 100 M	SCMC	PVA Cold
F1	+	+	+
F2	+	+	_
F3	+	_	+
F4	+	_	_
F5	_	_	+
F6	_	+	+
F7	_	+	_
F8	_	_	_

Table 3: Formulation table of loperamide hydrochloride loaded fast dissolving oral film.

Ingredients	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
Drug (mg)	2	2	2	2	2	2	2	2
HPMC K 100 M (mg)	200	200	200	200	130	130	130	130
SCMC (mg)	150	150	50	50	50	150	150	50
PVA Cold (mg)	150	50	150	50	150	150	50	50
Sodium saccharin (mg)	100	100	100	100	100	100	100	100
Citric acid (mg)	200	200	200	200	200	200	200	200
Propylene glycol (1ml)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Orange oil (1ml)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Sunset yellow	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Distilled water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

EVALUATION

Morphological properties[8]

Visual observation was evaluated for the appearance of films such as color, homogeneity, transparency, and the feel of touch.

Weight determination[9]

Three films of each formulation were randomly selected and weighed individually and the mean weight of films of each batch was calculated.

Thickness test[10]

A micrometer screw guage is used to measure the thickness of the oral film. The thickness is measured at 5 different locations to obtain uniformity of films. 4 corners of the film and center were selected for the measurement of the thickness.

Tensile strength[11]

The tensile strength is the property of the film that requires a load to cause load deformation failure of the film. Evaluated this mechanical property by using the test instrument. Film strip in special dimension and free from air bubbles or physical imperfection were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamp. The force and elongation were measured when the film broke. Results from film samples, which broke at and not between the clamps, were not included in the calculations. Measurements were run in triplicate for each film. Tensile strength is also defined as the maximum stress applied to a point at which the film or strip specimen breaks. The tensile strength of the film can be calculated by the formula as given below.

Tensile strength (TS) = (Load at failure*100)/ (Strip thickness *strip width)

Folding endurance[11]

Folding endurance is determined by repeatedly folding of the film strip at the same place till the film strip breaks. The number of times the film is folded without breaking computed as the folding endurance value.

Percentage moisture absorption[12]

The percentage moisture absorption (PMA) test was carried to check the physical stability of the fast dissolving oral film at high humid conditions. Three films were taken, weighed accurately and placed in a desiccator containing a saturated solution of aluminum chloride, keeping the humidity inside the desiccators. After 72 hours the films were removed, weighed and PMA was calculated by using the formula.

PMA = [(Final weight-Initial weight)/(Initial weight)]*100

Percentage moisture loss[12]

Percentage moisture loss (PML) was calculated to check the integrity of film at the dry condition. Three $1cm^2$ films were cut out and weighed accurately and kept in desiccators containing fused anhydrous calcium chloride. After 72 hours the films were removed and weighed. The percentage moisture loss was calculated by using the following formula.

PML = [(Initial weight-Final weight)/(Initial weight)]*100

Surface pH test[13,14]

The film to be tested was placed in a petridish and was moistened with 0.5 ml of distilled water and kept for 1 hour. The pH was noted after bringing the electrode of the pH meter in

contact with the surface of the formulation and kept for 1 minute to allow equilibrium condition. The procedure was performed in triplicate and average with standard deviation was determined.

Content uniformity[15,16]

Standard solution

Standard solutions prepared by taking 2 mg of loperamide hydrochloride in 100 ml of 0.01 N HCl. From this 1ml taken and diluted with 10 ml of 0.01 N HCl. Then the absorbance was measured at 214 nm.

Test solution

Three films were taken from each formulation and dissolve in 100 ml of 0.01 N HCl. Then the solution was filtered through Whatman filter paper. From the filtrate, the 1ml solution was taken and diluted with 10 ml of 0.01N HCl. The absorbance was measured at 226 nm. Content uniformity was calculated using following formula.

% Label claim = (Abt/Abs)*(Ds/Dt)*(100/Lc)*100

Abt = Absorption of sample or test solution

Abs = Absorption of standard solution

Ds = Dilution of standard

Dt = Dilution of sample or test

Lc = Labelled claim

Disintegration test[17]

Disintegration test of fast dissolving oral film of loperamide hydrochloride requires disintegration test apparatus. The disintegration time limit of 30 seconds or less for orally disintegration tablet described in the center for drug evaluation and research (CDER) guidance can be applied to fast dissolving oral strip. Disintegration time will vary depending on the formulation but typically the disintegration range from 5 to 30 seconds. The in vitro disintegration time of fast dissolving films was determined visually in a glass dish of 25ml distilled water or simulated saliva with swirling action. Disintegration time is defined as the time at which a film breaks when it comes in contact with the saliva.

In-vitro dissolution study[18,19,20]

In-vitro dissolution of loperamide hydrochloride fast dissolving oral film was carried out in USP paddle dissolution test apparatus using 900ml of 0.01N HCl as the dissolution medium the temperature was maintained at 37^{O}C throughout the experiment. 10ml sample was withdrawn at 1, 2, 3, 4, 5, 10, 20 and 30 minutes intervals and same quantity were replaced with 0.01N HCl. The cumulative percentage of drug released was determined using UV-Visible spectrophotometer at 214 nm.

SELECTION OF OPTIMIZED FORMULATION[21]

From the formulation F1 to F8, film F7 containing HPMC K100 M (130 mg), SCMC (150nmg), PVA cold (50 mg), sodium saccharin (100 mg), citric acid (200 mg), propylene glycol 1 ml, sunset yellow and orange oil in sufficient quantity were selected as the optimized formulation. Selection of optimized formulation done by considering the following parameters

- Drug content uniformity studies.
- *In vitro* disintegration time
- *In vitro* dissolution test

Stability studies of optimized formulation[22,23]

Stability studies of the promising formulation were done by subjecting the films from the optimized formulation at 40^{o} C temperature and 75± RH for one month. After 1 month, samples were withdrawn and evaluated for physical appearance, disintegration time, drug content, folding endurance, weight uniformity and percentage cumulative drug release.

Kinetic analysis of *in vitro* release data[24,25,26]

The in-vitro release data of the drug from the investigated fast dissolving oral films, the optimized formulation was analyzed by curve fitting method to different kinetic model of Zero order, First order, Higuchi model, and Korsmeyer-Peppas models.

- **First order model**

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by the equation:

$$\frac{dC}{dt} = -Kc$$

where K is first order rate constant expressed in units of time^{-1}. The above equation can be expressed as:

log C = log C_0-Kt / 2.303

where C_0 is the initial concentration of the drug, k is the first order rate constant, and t is the time. The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of -K/2.303.

- ***Zero order*** kinetics where the drug release rate is independent of its concentration. For study of release kinetics, the graph plotted between Percentage cumulative drug release (CDR) vs Time

$$C = C_0 - K_o t$$

Where,

C- Amount of drug released

C_0- Initial concentration of drug

K_0- Zero order rate constant

t- Time

- ***Higuchi model*** which describes drug release from insoluble matrix system. The data obtained were plotted as cumulative percentage drug release (%CDR) vs square root of time (t^2)

$$Q = K_H t^{1/2}$$

Where, Q- Amount of drug released

K_H- Higuchi release constant

t- Time

- ***Korsmeyer-Peppas model*** was used to find out the mechanism of drug release from the vesicular formulations. The plot made by log cumulative percentage drug release (log %CDR) vs log time (log t).

$$M_t/M_\infty = Kt^n$$

Where, M_t/M_∞- Drug released at a time t

K- Release rate constant

n- Release exponent

In this model, the value of 'n' characterizes the release mechanism of the drug.

RESULTS AND DISCUSSION

PREFORMULATION STUDIES

Characterization of Loperamide hydrochloride

Table No. 4: Characterization of loperamide hydrochloride

Test	Specification/limits	Observations
Color	White powder	White powder
Taste	Bitter	Bitter
Odor	Odorless	Odorless

Table No. 5: Solubility of Loperamide hydrochloride.

Solvents	Inference
Water	Slightly soluble
Chloroform	Freely soluble
Ethanol	Freely soluble
Methanol	Freely soluble
Isopropyl alcohol	Freely soluble

Calibration curve of loperamide hydrochloride

The calibration curve of loperamide hydrochloride was determined at 214 nm by plotting absorbance against concentration. The calibration curve shown in Figure 1 was found to be linear between 2-12 µg/ml.

Table No. 6: Absorbance for calibration curve.

Concentration (µg/ml)	Absorbance (nm)
0	0.000
2	0.032
4	0.050
6	0.078
8	0.101
10	0.125
12	0.150

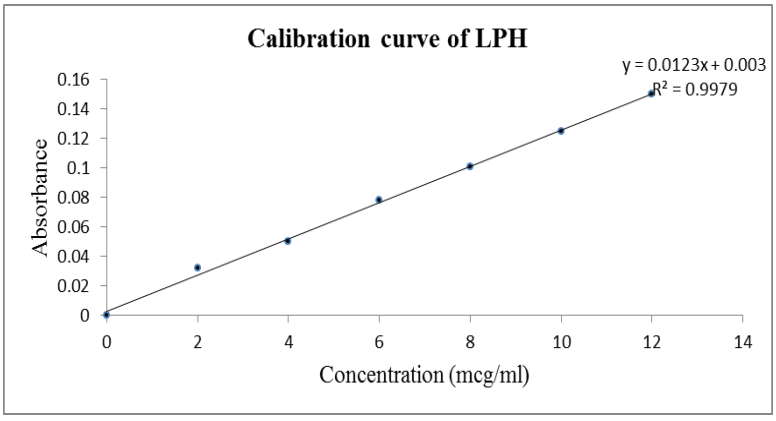

Figure 1: Calibration curve of loperamide hydrochloride.

FT-IR Analysis

The FT-IR spectrum of pure drug exhibits characteristic absorption peaks at M 3241.75 cm^{-1} (OH, alcohol, phenol hydrogen bond), S 1621.84 cm^{-1} (CONH), 1475 cm^{-1} (aromatic C=C), W 1373 cm^{-1} (C-N amine), S 971 cm^{-1} (alkene) and S 747 (Cl).

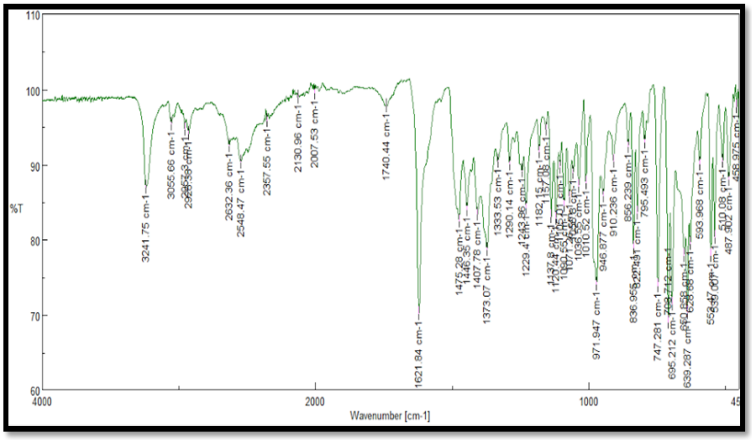

Fig. 2: FT-IR spectrum of Loperamide hydrochloride (LPH).

The spectrum of drug and physical mixtures shows characteristic absorption bands of S 1738 cm^{-1} (C=O ester, aldehyde), W 1620 cm^{-1} (C=C alkene), M 1367 cm^{-1} (C-N amine), M 1213 cm^{-1},1228 cm^{-1} (NH bond) and W 1034 cm^{-1} NH amine.

(Where W:Weak, M:Medium and S:Strong)

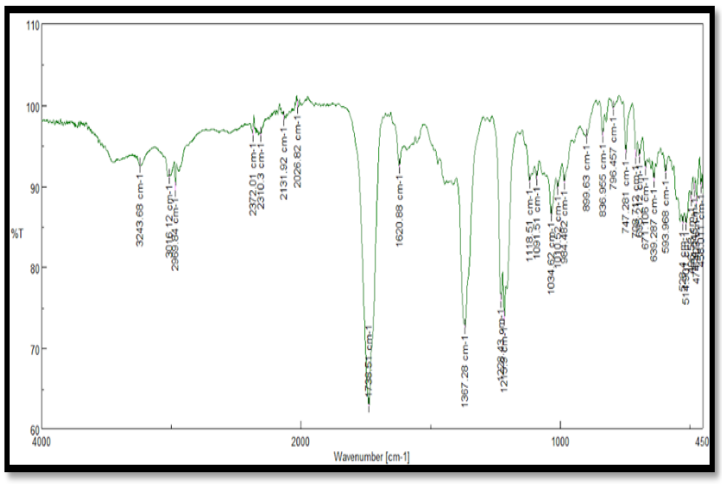

Fig. 3: FT-IR spectrum of drug and excipients.

Results were confirmed that characteristic absorption peaks of the pure drug have appeared in the spectra of its physical mixtures without any significant change in their position and its values.

Morphological properties

The visual inspection was done on all batches of films made from a different combination of polymers like hydroxyl propyl methyl cellulose K100 M, Sodium carboxy methyl cellulose, poly vinyl alcohol cold. The films made from these polymer combinations showed good appearance and were stable remaining without any change in their properties.

Table No. 7: Morphological properties of prepared film.

Formulation code	Color	Transparency	Homogeneity	Feel of touch
F1	Light orange	Semi-transparent	Homogenous	Smooth and dry
F2	Light orange	Semi-transparent	Homogenous	Smooth and dry
F3	Light orange	Semi-transparent	Homogenous	Smooth and dry
F4	Light orange	Semi-transparent	Homogenous	Smooth and dry
F5	Light orange	Semi-transparent	Homogenous	Smooth and dry
F6	Light orange	Semi-transparent	Homogenous	Smooth and dry
F7	Light orange	Semi-transparent	Homogenous	Smooth and dry
F8	Light orange	Semi-transparent	Homogenous	Smooth and dry

Weight variations

The weight variations were measured for all the formulations and the results were given in table 3. Weight variation ranges from 0.005 to 0.02. From these results, it can be concluded that as the polymer concentration increases, weight also increased.

Film thickness

The thickness of the film directly influences the mass of film and content of drug loaded in it. The results for the different batches made with three different polymers in different concentrations are shown in figure 8.All the prepared films showed significant thickness when different polymers in different concentrations were used. Films made from the combination of HPMC K100 M (130mg), SCMC (150mg) and PVA Cold (50mg) were showed less thickness. Results suggested that film thickness decreases with a decrease in the polymeric concentrations.

Tensile strength

The results of tensile strength from various formulations (F1 to F8) are given in table 4. The tensile strength of all the films was in the range of 133.32±0.010 to 198.33±0.015 with very low values of standard deviations suggesting all films were having good mechanical strengths to withstand mechanical damage during, production and application.

Folding endurance

The folding endurance was measured manually. It measures the ability of the film to withstand rupture. The results indicated that the endurance increases on decreasing polymer content in the film. It varies from 199 to 252 times.

Percentage moisture absorption

The percentage amount of moisture absorbed by the film preparation was given in the table no: 6. The results indicated that the ability of the preparation to absorb moisture at normal conditions. It also gives an idea about hydrophilic nature of the preparation. Percentage moisture absorption for all the formulations ranged from 0.162±0.007 to 0.500±0.006 at room temperature.

Percentage moisture loss

The results of % moisture loss of various films are given in table 7. The results indicate that % moisture loss of films was in the range of 0.020 to 0.154 at room temperature. The standard deviation values were very less suggesting that the drug lost low moisture content.

Surface pH test

The pH of the films was determined in order to investigate the possibility of any side effects *in vivo*. The pH values of films made from a different combination of polymers are given in table 8. As an acidic or alkaline pH may cause irritation to the oral mucosa, it was determined to keep the surface pH to neutral as close as possible. The neutral pH shown for the films assured that there will not be any kind of irritation to the mucosal lining of the oral cavity. All formulated films showed much closed to neutral pH.

Content uniformity of drug

The drug contents in the films were found to be between 88.36 to 96.10 %. As per the USP requirements, the films found to meet the criteria for content uniformity 85-115 % of the labeled claim. All the preparations met the criteria of USP content uniformity. On this basis, it was found that the drug was dispersed uniformly throughout the film of $1cm^2$.

Disintegration test

The results of disintegration times of various formulations (F1 toF8) are given in table 10. All the films were showing disintegration time in the range of 50-62 seconds. Results revealed that the disintegration time changes based on the concentration and the type of polymers.

Table No. 8: Values of various evaluation test.

Formulation code	Mean weight(g)±S.D	Thickness (mm)	Tensile strength (g/cm^2)	Folding endurance value (no: of times)	% Moisture absorption
F1	0.0218±0.04	0.246±0.011	198.33±0.015	223±1.52	0.310±0.005
F2	0.0191±0.05	0.230±0.010	166.68±0.025	200±1.32	0.235±0.003
F3	0.0188±0.04	0.240±0.010	173.91±0.005	199±2.02	0.246±0.004
F4	0.0122±0.05	0.156±0.005	187.52±0.010	205±1.73	0.220±0.003
F5	0.0123±0.04	0.153±0.005	133.32±0.010	225±0.56	0.232±0.007
F6	0.0186±0.05	0.233±0.005	173.97±0.010	228±1.22	0.248±0.005
F7	0.0128±0.05	0.143±0.011	166.48±0.025	241±0.88	0.231±0.002
F8	0.0081±0.05	0.110±0.010	133.71±0.005	252±0.93	0.224±0.006

Table No. 9: Dissolution test.

Formulation code	% Moisture loss	pH	Content uniformity of drug	Disintegration time (seconds)
F1	0.082±0.007	6.95±0.014	88.36±0.015	62.00±1.00
F2	0.062±0.001	7.06±0.014	93.14±0.011	56.66±1.52
F3	0.059±0.005	6.91±0.007	94.14±0.015	56.33±0.50
F4	0.046±0.001	6.73±0.014	95.33±0.025	53.33±1.15
F5	0.044±0.005	7.04±0.021	95.13±0.026	51.66±0.57
F6	0.066±0.005	6.82±0.007	94.45±0.030	59.33±0.57
F7	0.017±0.007	6.83±0.007	96.10±0.011	50.33±0.57
F8	0.022±0.007	6.94±0.014	92.83±0.020	61.66±1.15

Dissolution test

It can be seen from the table 11 and figure 14 that the cumulative % drug release from the formulations F1, F2, F3, F4, F5, F6, F7 and F8 was found to be 47.65, 66.09, 79.93, 95.30, 94.12, 84.54, 96.84 and 83.00 at the end of 30 min respectively. The results suggest that polymers with different concentrations play an important role in the release of drug from the films. Formulation F7 showed the highest value of drug release of 96.84%.

Table no.20: Percentage cumulative drug release of prepared fast dissolving oral films.

Time (min)	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
1	13.83 ±0.81	19.98 ±0.66	7.68 ±0.98	12.29 ±0.67	10.76 ±0.43	15.37 ±0.55	13.83 ±0.88	7.68 ±0.12
2	15.37 ±0.75	23.05 ±0.54	24.59 ±0.80	16.90 ±0.77	13.83 ±0.48	23.05 ±0.76	23.05 ±0.60	10.76 ±0.34
3	19.98 ±0.34	24.59 ±0.56	29.20 ±0.57	23.05 ±0.76	24.59 ±0.86	30.74 ±0.59	35.35 ±0.63	13.83 ±0.56
	27.66	27.66	33.81	27.66	35.35	46.11	42.27	16.90

4	±0.25	±0.98	±0.86	±0.80	±0.75	±0.39	±0.77	±0.61
5	30.74 ±0.69	29.20 ±0.71	38.42 ±0.47	36.89 ±0.68	44.57 ±0.59	61.48 ±0.75	50.72 ±0.90	24.59 ±0.58
10	35.35 ±0.88	36.89 ±0.52	46.11 ±0.91	47.65 ±0.45	59.94 ±0.76	76.85 ±0.48	66.09 ±0.78	49.18 ±0.68
20	38.42 ±0.63	53.80 ±0.65	64.56 ±0.82	69.17 ±0.61	84.54 ±0.70	79.93 ±0.44	89.15 ±0.94	73.78 ±0.47
30	47.65 ±0.73	66.09 Values are expressed in mean ± SD, (n=3) ±0.89	79.93 ±0.54	95.30 ±0.76	94.12 ±0.59	84.84 ±0.19	96.84 ±0.79	83.00 ±0.58

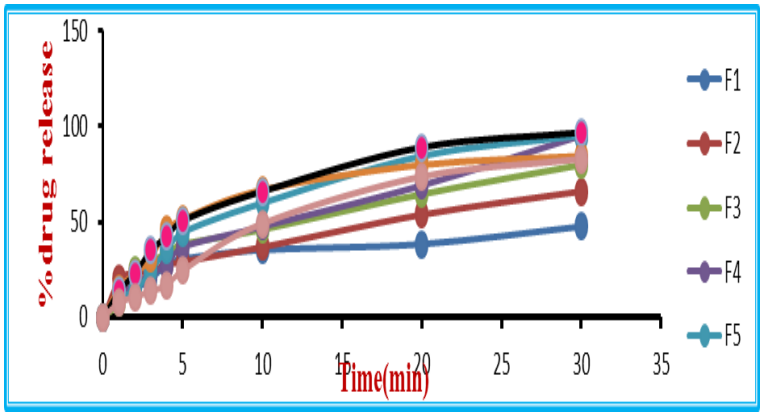

Fig. 4: Comparative Evaluation of % Drug release of All Formulations.

Stability study of the optimized formulation.

The promising formulation F7 was subjected at a 40±0.5^{0}C temperature and 75±5%RH for 1 month to check the stability. The results of physical appearance, drug content, Disintegration time and other parameters after one-month storage of prepared fast dissolving films shown in table 12 and % drug release is shown in table 13.

Table No. 10: Stability study of promising batch F7.

Parameter	At 0 days	After 30 days
Appearance	Light orange	No change
Disintegration time	50.33±0.57	54.58±0.54
Drug content	96.10±0.011	92.81±0.03
Folding endurance	241±0.88	238±0.62
Weight uniformity	0.0128±0.05	0.0119±0.05

Table No. 11: Percentage cumulative drug release after stability study.

Time(min)	% cumulative drug release	
	At 0 days	At 30 days
0	0.00±0.00	0.00±0.00
1	13.83±0.12	10.62±0.28
2	23.05±0.34	21.16±0.47
3	35.35±0.56	33.14±0.39
4	42.27±0.61	40.65±0.53
5	50.72±0.58	47.81±0.48
10	66.09±0.68	63.53±0.59
20	89.15±0.47	86.32±0.67
30	96.84±0.58	93.73±0.23

Values are expressed in mean ± SD, (n=3)

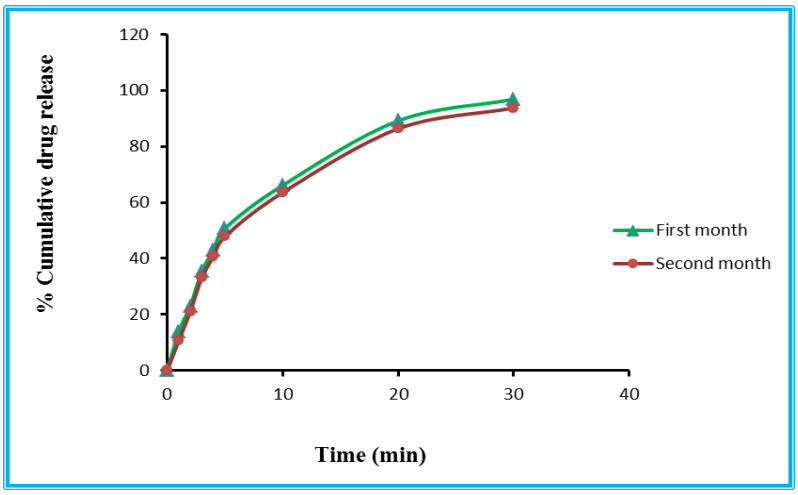

Figure no.5: Percentage cumulative drug release after stability study.

Kinetic analysis of in-vitro release data of optimized formulation F7

Table No. 12: *In-vitro* drug release data of formulation F7.

S.No	Time (min)	Square root of time	Log time	Cumulative Percentage Drug release	Log of cumulative percentage drug release	cumulative percentage drug remain	Log of cumulative percentage drug remain
1	1	1.0000	0.0000	13.8345	1.14096	86.1655	1.93533
2	2	1.4142	0.3010	23.0574	1.36281	76.9426	1.88617
3	3	1.7320	0.4771	35.3547	1.54845	64.6453	1.81054
4	4	2.0000	0.6020	42.2720	1.62605	57.728	1.76139
5	5	2.2360	0.6989	50.7264	1.70523	49.2736	1.69261
6	10	3.1622	1.0000	66.0980	1.82019	33.902	1.53023
7	20	4.4721	1.3010	89.1554	1.95015	10.8446	1.03521
8	30	5.4772	1.4771	96.8412	1.98606	3.15878	0.49952

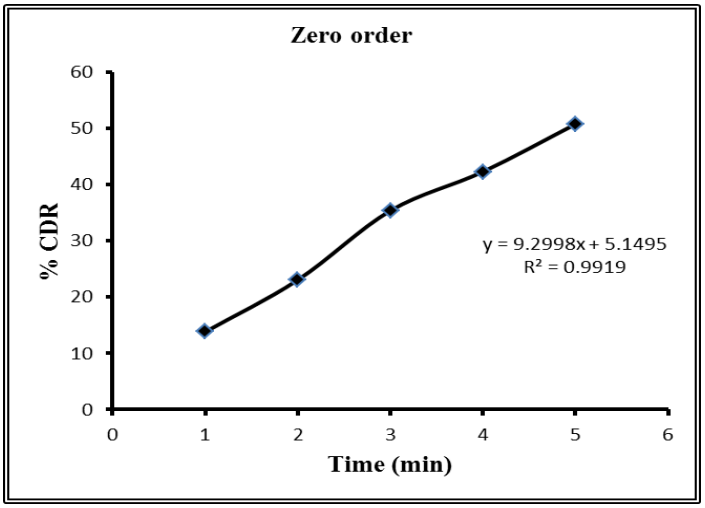

Fig No. 6: Zero order release kinetics of optimized formulation F7.

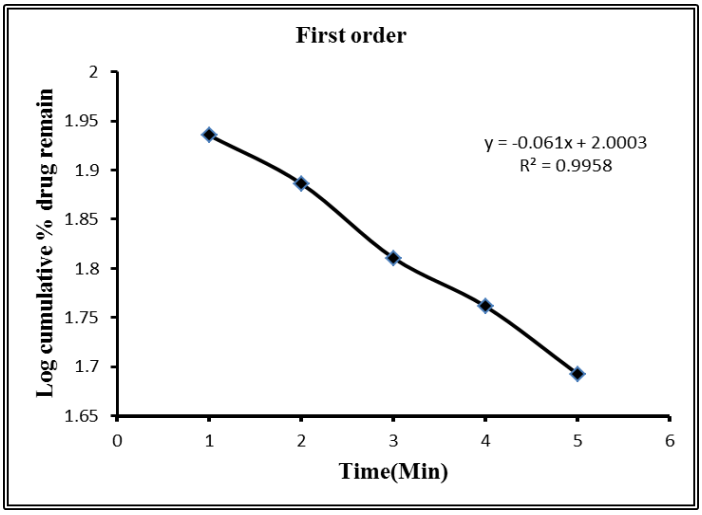

Fig No. 7: First order release kinetics of optimized formulation F7.

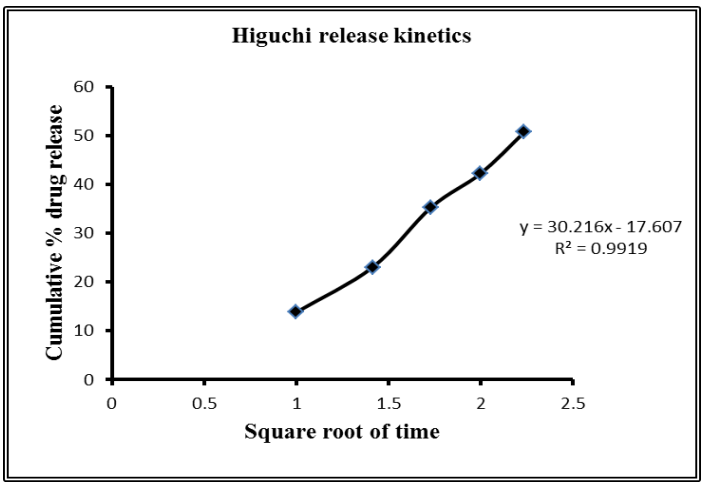

Fig. No. 8: Higuchi release kinetics of optimized formulation F7.

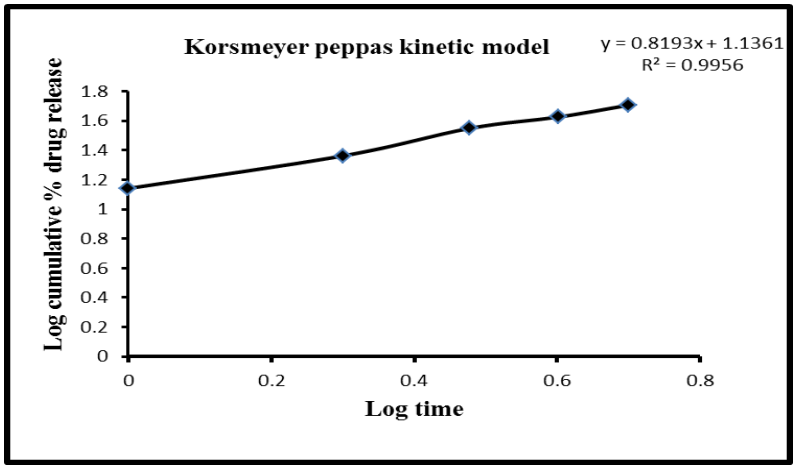

Fig No. 9: Korsmeyer peppas release kinetics of optimized formulation F7.

Table No: 13. Kinetic data of optimized formulation F7.

Formulation code	Regression coefficient	Zero order	First order	Higuchi	Peppas
F7	r^2	0.9919	0.9958	0.9919	0.9956

In order to determine the release mechanism that provides the best description to the pattern of drug release, the in vitro release data were fitted to zero order, first order, Higuchi model, and Korsmeyer-peppas model. After undergoing the release model for optimized formulation the in vitro drug release of the optimized formulation F7 was best explained by first order, as the plots showed the highest linearity (r^2=0.9958), followed by zero order (r^2=0. 9919), Higuchi (r^2=0.9919) and Korsmeyer-peppas (r^2=0.9956).

CONCLUSION

Several fast dissolving oral films have already been entered in the market. Oral films are relatively easy to fabricate because the preparation was found to be simple requiring minimum excipients thus making the product cost effective. Being consumer-friendly alternatives, this delivery platform shows commercial potential capacity or wider scope for future in pharmaceuticals. The present investigation was evidence that the polymer based oral film may be a promising tool for anti-diarrhoeal treatment to the patients. The results further supported the possibility of the drug with novel formulation technology to develop better, effective, safer and economical product. Modern formulation and analytical techniques may be helpful to overcome the experimental errors.

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