FORMULATION AND EVALUATION OF LOPERAMIDE ORAL FILMS

I. Amar Sandeep*,N. Bhavana, P.T.Sankeerth, P.Nandhini, Rama Rao Nadendla.

Department of industrial pharmacy, Chalapathi institute of pharmaceutical sciences, Lam, Guntur.

ABSTRACT:
Loperamide is a synthetic opioid that does not have any central nervous action in therapeutic doses. It binds with intestinal μ-receptors and thus causes an alteration of the neuronal activity of the intestinal motility. The results are a reduction of the propulsive peristalsis and a reinforcement of the rhythmic pendulum movement (the intestinal transit time). Loperamide causes a prolonged passage, a thickening of the stool, and a decrease of fluid and electrolyte losses. The tone of the anal sphincter is also increased. Loperamide probably also has anti secretory activity. Fast dissolving sublingual films of loperamide were prepared by solvent casting method. Water soluble polymer hydroxyl propyl methyl cellulose E50 & E5 were used as film forming polymer. propylene glycol was used as plasticizers. Sucrose was added as a sweetener and menthol as flavoring agent. The formulations prepared were evaluated for their uniformity of weight, surface pH, folding endurance, disintegration time, tensile strength, % elongation, content uniformity and % drug release. The FTIR studies showed no interaction between drug and polymer. From the observations of evaluation results, it was concluded that formulation F2 containing 0.2ml PG for films prepared using HPMC E 50 having sodium starch glycolate as super disintegrants is found to be the best formulation among the all other formulations.

Results: . The drug loperamide found to feasible to develop into oral flash films. The method solvent casting adopted for the formulation of loperamide oral films is convenient and economical. The super disintegrants employed in this work found to appreciable. The drug-excipient compatibility by FT-IR studies revealed no physicochemical interaction. The oral films obtained found clear, enough physical strength and showed reasonable degree of disintegration time. The in vitro dissolution studies of all the formulations in contrast of pure drug showed better release profile. . From the observations of evaluation results, it was concluded that formulation F2 containing 0.2ml PG for films prepared using HPMC E 50 having sodium starch glycolate as super disintegrants is found to be the best formulation among the all other formulations.

Keywords: Loperamide, oro flash films, FT-IR, In-vitro dissolution studies**.**

INTRODUCTION:

Many pharmaceutical dosages are administered in the form of pills, granules, powders, and liquids. Generally, a pill design is for swallowing intact or chewing to deliver a precise dosage of medication to patients. The pills, which include tablets and capsules, are able to retain their shapes under moderate pressure. However, some patients, particularly paediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms Many paediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking. Hence, orally dissolving tablets have come into existence. Even with these differences, most of the existing oral dissolving drug delivery systems are in the form of solid tablets and designed to dissolve/disintegrate in the patient's mouth without the need to drink or chew. However, the fear of taking solid tablets and the risk of choking for certain patient populations still exist despite their short disintegration/ dissolution times. Hence oral film drug delivery is a better alternative in such cases. The oral availability of many drugs is poor because of the pH of the stomach, the presence of enzymes, and extensive first-pass metabolism. Traditionally, these drugs were being administered as parenteral drug delivery systems, which invariably lead to poor patient compliance. This has made the pharmaceutical industry look for alternative routes of drug delivery like film drug delivery. Intraoral fast dissolving drug delivery system is placed on the top or the floor of the tongue. The formulation is retained at the site of application and rapidly releases the active agent for local or systemic absorption [1].

*Correspondence:
I. AMAR SANDEEP,
Department of industrial pharmacy,
Chalapathi institute of pharmaceutical sciences, Lam,
Guntur.Andhpradesh-522034
Email: amarsandeep095@gmail.com

MATERIALS AND METHODS:

MATERIALS	CATEGORY	PROCURED FROM
Loperamide	Anti-Diarrheal	Apotex laboratories, Bengaluru.
HPMC-E50 LV	Film Forming Polymer	LOBA Chemie Pvt. Ltd. Mumbai.
HPMC E5 LV	Film forming polymer	LOBA Chemie Pvt. Ltd. Mumbai
Propylene Glycol	Plasticizer	LOBA Chemie Pvt. Ltd. Mumbai
Citric Acid	Saliva Stimulating Agent	Thermo Fisher Scientific India Pvt. Ltd. Mumbai
Sodium Starch Glycolate	Super Disintegrant	LOBA Chemie Pvt. Ltd. Mumbai
Cross povidone	Super Disintegrant.	Thermo Fisher Scientific India Pvt. Ltd. Mumbai
Sucrose	Sweetener	Thermo Fisher Scientific India Pvt. Ltd. Mumbai
Menthol	Flavoring agent	Thermo Fisher Scientific India Pvt. Ltd. Mumbai
Synthetic food colors	Coloring agent	Commercial sources

Table 1:- formulation ingredients of loperamide oro flash films

Instruments used:
Analytical balance .
Dissolution apparatus.
Film former.
Uv visible spectrophotometer.

Data handling systems:
UV-win for the handling of spectrophotometer.
Microsoft excel.

Materials used:
Working standards of drugs were procured from Apotex laboratory.
Commercial formulation of drugs was purchased from local market. Sodium starch glycolate was procured from loba chem pvt (India) ltd, Mumbai.

.Preformulation studies:-

3.1)Ft-ir studies:-
FTIR studies was conducted using FTIR instrument on pure loperamide drug and with the mixture of polymers in numerous ratios to search out the compatibility and found to be compatible with all ingredients. [17,18]

FORMULATION METHODOLOGY OF LOPERAMIDE ORO FLASH FILM:

Loperamide oral films were prepared with six completely different compositions. During which the impact of super disintegrants and polymers on the speed of dissolution is studied. The formulations were prepared as per the table no.2. During this methodology, drug is casted with polymer and all other ingredients without any entrapped bubbles. The drug was dissolved in in 1/4th amount of 25ml water polymer and water mixture. Then, the drug-polymer solution is, added with other ingredients. Once, the swelling obtained, it had been casted on the film former equipment with spreader. The temperature of the equipment maintained at 50°C. The casted solution is, maintained for 6hrs and peeled off from the equipment. Then, the film is transferred to the desiccators for further studies. [5,9]

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
loperamide (mg)	50	50	50	50	50	50
Hydroxy propyl methylcellulose (HPMC)-E50 LV (%)	5	5	-	-	-	5
Hydroxy propyl methylcellulose (HPMC)- E5 LV (%)	-	-	6	6	6	-
Propylene glycol (ml) (PG)	0.2	0.2	0.2	0.2	0.2	0.2
Sodium starch glycolate-Primojel (%) (SSG)	2	6	8	-	-	-
Cross povidone(%) (CPV)	-	-	-	2	4	6
Citric acid (mg)(%W/W)	0.5	0.5	0.5	0.5	0.5	0.5
Menthol(ml)	2	2	2	2	2	2
Purified water (ml) q.s	25	25	25	25	25	25

Table no.2. formulation table of loperamide oro flash films.

EVALUATION TESTS FOR ORO FLASH FILMS

Weight variation test:

Ten films are picked randomly from each formulation batch. The mean weight of film as well as the deviation from the mean was calculated and recorded.[19,20]

Transparency:

It can be determined using a simple UV – Visible spectrophotometer. This determines the transmittance of films at 600 nm. The transparency of film is calculated by using formula.[18,7,8]

Transparency = (log T600) / b = -εc

Where, T600= transmittance at 600 nm

b= film thickness (mm)

c= is concentration. [14,16]

Thickness of film:

Thickness of film is measured using dial gauge or Vernier callipers or screw gauge or microscope. Thickness at different points measured from which the average thickness of film is determined. [11,13]

Folding endurance:

The folding endurance determined by repeatedly folding one film at the same place until it broke. The number of times the film folded at the same place without breaking or cracking gives the value of folding endurance. Folded up to 300 times which is satisfactory to reveal good film properties. [4,6]

Surface pH of film:

The surface pH of film was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the oral mucosa. It was determined to keep the surface pH as close to neutral as possible. The films allowed for swelling in closed Petri dish at room temperature for 30 minutes. In that, 1ml of solution placed under digital pH meter to determine the surface pH of film. [3,10]

Water uptake test or swelling study:

The film sample was taken weighed and placed on a pre-weighed stainless steel wire mesh. The wire mesh is submerged in a Petri dish containing 40 ml of 6.8 phosphate buffer. Increase in weight of film was determined at regular time intervals until constant weight is obtained. The hydration ratio of the film was calculated using following formula. [1,19]

Swelling index (SI) = (Wt – W0) /W0

Where, Wt = weight of film at't' time

W0 = weight of film at '0'time

Drug content or drug uniformity:

The drug content and uniformity test was performed to ensure uniform and accurate distribution of d rug. Each film dissolved in 50 ml volumetric flask containing methanol. Then solution was filtered through what Mann filter paper No. 41. Aliquot of a 1 ml of filter solution taken into 25 ml of volumetric flask made up to 25 ml with 6.8 phosphate buffer. Then solution analyzed by U.V spectrophotometer at 223nm against in phosphate buffer pH 6.8 solution as blank. [12,15]

In vitro disintegration test:

The disintegration time is the time when a film starts to break or disintegrate. The disintegration test of fast dissolving film was carried out using single unit disintegration apparatus containing 900 ml of 6.8 phosphate buffer. Switch on the disintegration apparatus and set temperature to 37.5 ± 0.5o C. After reaching, the temperature film is placed on disintegration apparatus time required to start break film is noted as disintegration time of particular film. [1,5]

In vitro Dissolution studies:

In vitro dissolution study can be performed using the 8-stage USP type –II apparatus paddle as per the pharmacopeia. Mainly paddle type dissolution was used to study the rate of drug dissolution test from the developed oral films. It is customary to assess the tendency of the strip to float on to the dissolution medium or not. In vitro dissolution can be performed by using USP- Type II apparatus (Disso 2000 with auto sampler) containing 6.8 phosphate buffer at the speed of 50 rpm with 37.5 ± 0.5o C. [19,20]

RESULTS AND DISCUSSIONS

Weight uniformity:

As not all batches have uniform amount of ingredient in it, hence their weight and thickness varied with each other. Weight uniformity of the films was found to be between 34.1±0.072mg to 77.0±0.144mg. The results are shown in Table no:3.

Thickness:

Thickness of the films was found to be between 0.0208±0.002mm to 0.299±0.005mm. A very low standard deviation values indicated that the method used for the formulation of film is reproducible and gave film of uniform thickness and hence dosage accuracy in each film can be ensured. The results are shown in Table no:3.

Surface pH:

Surface pH of all films found to be in the range of 6.53 to 6.80. All films found to be in the range of salivary pH. The results are shown in Table no: 3.

Formulation code	**Physical appearance**	**Surface texture**	**Weight uniformity (mg±SD)**	**Surface pH**	**Thickness (mm±SD)**
F1	Transparent	Very smooth	34.1±0.072	6.67	0.0208±0.002
F2	Transparent	Very smooth	46.2±0.057	6.80	0.145±0.004
F3	Transparent	Very smooth	57.1±0.173	6.65	0.199±0.004
F4	Transparent	Very smooth	63.4±0.11	6.76	0.283±0.003
F5	Transparent	Very smooth	41.3**±0.3**	6.79	0.1 ± 0.02
F6	Transparent	Very smooth	52.2 ± 0.65	6.72	0.16 ± 0.01

Table no 3. Evaluation tests of loperamide oro flash films.

Percentage moisture loss and percentage moisture absorption

The study of percentage moisture loss and percentage moisture absorption gives the idea about the stability of the film in different environmental conditions. More the moisture absorption property of the film less stable it will be. However, it found that % moisture absorption and percentage moisture loss was found to be appreciable with the use of hydrophilic polymer HPMC. Percentage moisture loss was found to be between 1.23 to 3.91and Percentage moisture absorption was found to be between 2.21 to 5.87 .The results are the shown in Table no:4.

Disintegration time

The disintegrating time limit of 30seconds or less for orally disintegrating tablets described in CDER guidance are applied to fast dissolving oral films. Although, no official guidance is available for oral fast disintegrating film, it can be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeia disintegrating time for films is 5-30 sec. The in-vitro disintegration time of the films found to be between 10±0.31 to 58±0.45sec. Study showed that disintegration time increased with increase in the polymer concentration. The results are represented in Table no:4.

Drug content

Drug content of the films was found to be between 97.62±0.011% to 100.01±0.063%. The observed result indicate that the drug was uniformly dispersed throughout the film. The results are shown in Table no: 4.

Formulation code	%Moisture loss (X±SD)	Disintegration time (sec) (X±SD)	%Drug content (X±SD)	Folding endurance (X±SD)

F1	1.23	2.61	97.62±0.011	262±2
F2	1.85	3.48	99.04±0.022	243±5
F3	2.63	4.98	98.86±0.034	272±6
F4	2.95	5.01	99.03±0.005	281±3
F5	2.75	4.56	95.86±0.022	301±3
F6	2.22	5.99	98.86±0.025	265±3

Table no 4 Evaluation tests of loperamide oro flash films.

Physical appearance and surface texture of films: 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 no:3 and it is shown in FIG.NO.1,2,3.

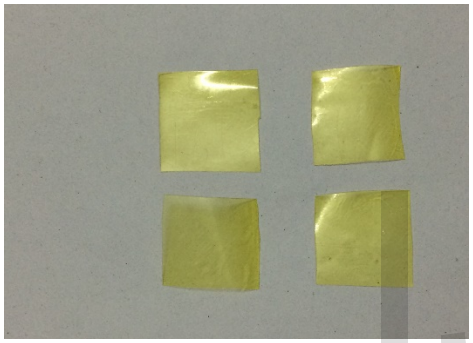

FIG.NO.1 (F2)

FIG.NO.2 (F2)

FIG.NO.3 F3, F4, F5, F6

FT-IR Studies

Compatibility studies for the films were performed using the FT-IR studies and the compatibility was confirmed which were shown in the fig no 4,5,6,7,8.

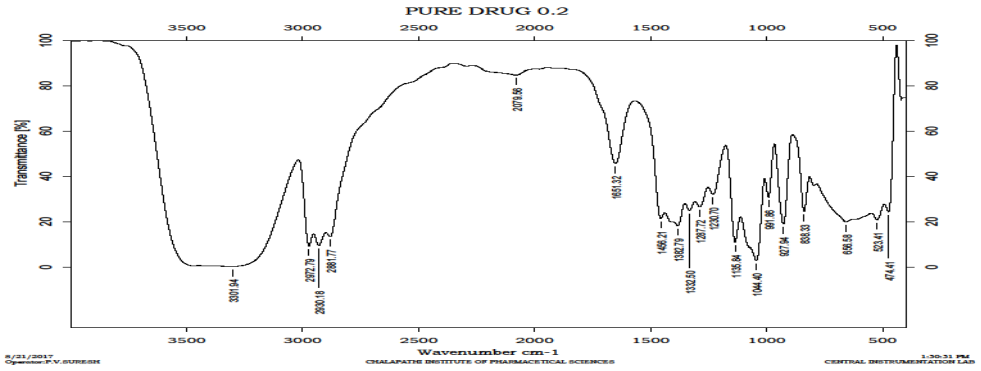

FIG.NO.4 FT-IR of loperamide pure drug.

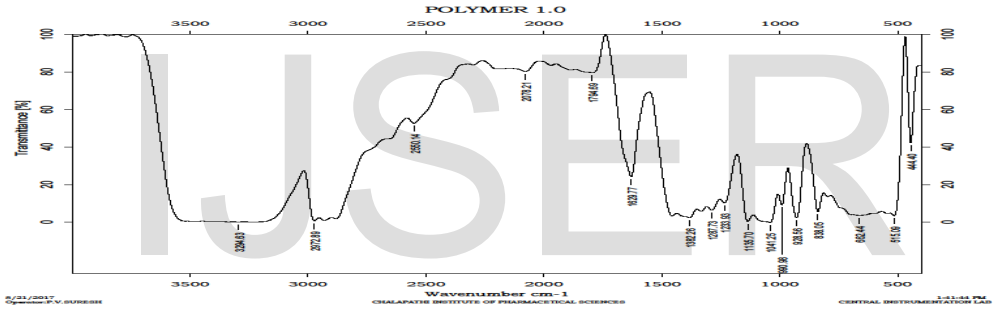

FIG.NO.5 FT-IR spectrum of loperamide oro flash film using HPMC E50 LV polymer and SSG .

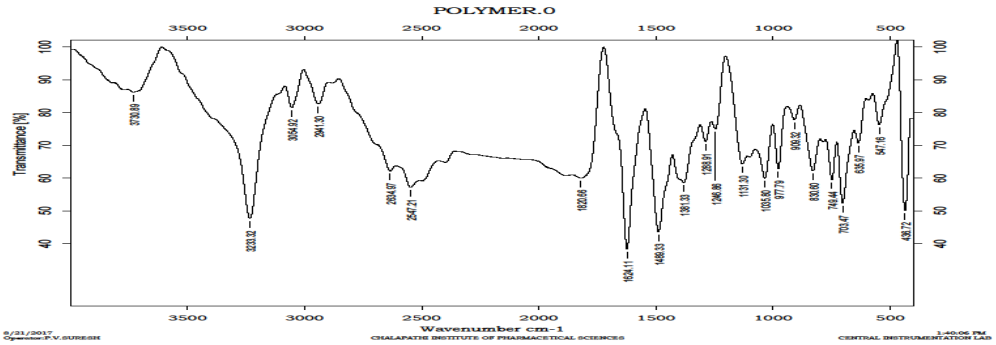

FIG.NO.6 FT-IR spectrum of loperamide oral flash film using HPMC E50 LV and CPV,

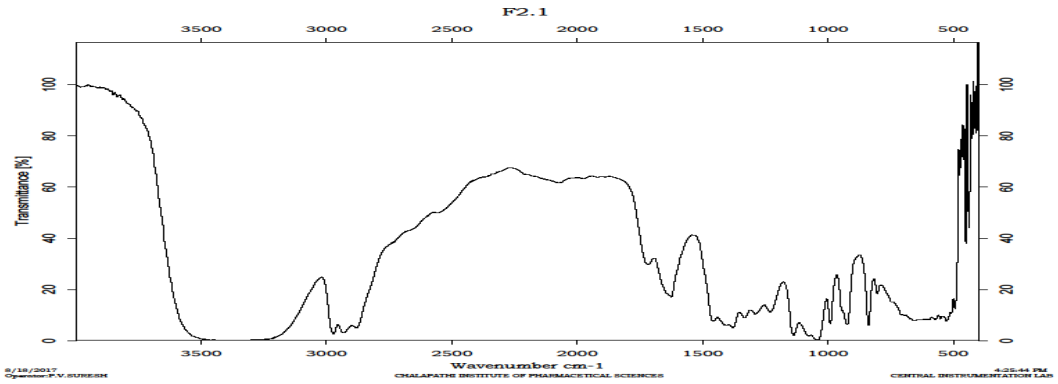

FIG.NO.7 FT-IR spectrum of LOPERAMIDE oro flash films using HPMC-E5 polymer and SSG.

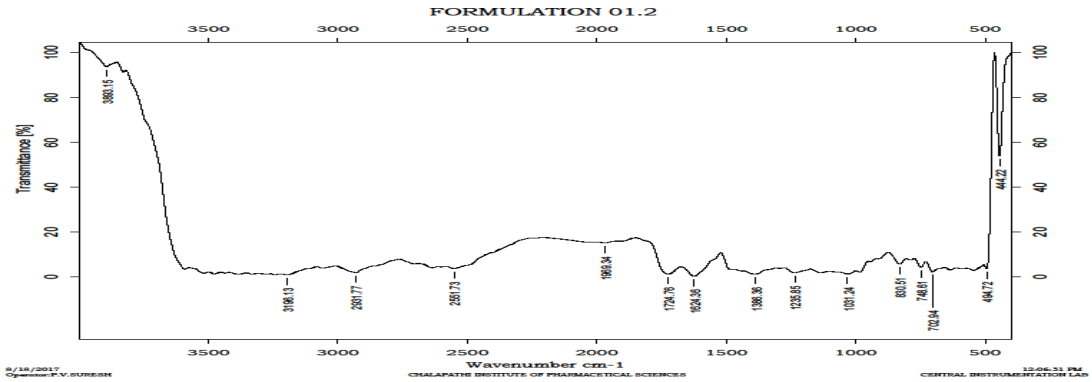

FIG.NO.8 FT-IR spectrum of LOPERAMIDE oro flash film using HPMC E5 polymer and CPV.

In vitro release studies

Dissolution study indicates the rate and extent of absorption. The in-vitro dissolution of loperamide films were carried out using 900ml phosphate buffer of pH 6.8 using USP II paddle type apparatus. In-vitro dissolution study for all the batches were performed for 5minutes. The results are shown in Table no.5

Cumulative % drug dissolution of loperamide films

Time (mins)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.5	36.2	56.4	46.7	58.2	42.8	46.4
1	44.5	88.8	78.1	86.9	62.7	58.9
1.5	52.3	90.6	80.2	89.1	85.8	74.3
2	64.8	95.6	82.3	92.2	91.4	85.8
2.5	72.5	98.1	84.5	94.8	93.6	89.6
3	76.1	99.5	86.0	97.0	94.3	94.7
3.5	78.4	99.0	89.9	98.2	95.5	96.9
4	82.2	99.1	92.4	98.6	96.4	97.8
4.5	84.5	99.3	94.6	98.9	97.0	98.4
5	86.8	99.4	97.3	99.0	97.2	98.8

Table.5. *In vitro* release studies of fast dissolving oral films of loperamide.

FIG.NO.9. dissolution profile of loperamide oro flash films.

CONCLUSION:

The following conclusions can be drawn from the obtained results. The drug loperamide found to feasible to develop into oral flash films. The method solvent casting adopted for the formulation of loperamide oral films is convenient and economical. The super disintegrants employed in this work found to appreciable. The drug-excipient compatibility by FT-IR studies revealed no physicochemical interaction. The oral films obtained found clear, enough physical strength and showed reasonable degree of disintegration time. The in vitro dissolution studies of all the formulations in contrast of pure drug showed better release profile. . From the observations of evaluation results, it was concluded that formulation F2 containing 0.2ml PG for films prepared using HPMC E 50 having sodium starch glycolate as super disintegrants is found to be the best formulation among the all other formulations.

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CONFLICT OF INTEREST

This is a non-funding research work. There were no conflicts of interest.

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