FORMULATION AND EVALUATION OF ORAL FAST DISSOLVING FILMS OF LANSOPRAZOLE BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

The goal of the present study was to develop and evaluate lanzoprazole fast-dissolving films. Lansoprazole (LAN) is an inhibitor of the proton pump used to treat stomach ulcers. In order to improve the drug's solubility, we developed Lansoprazole solid dispersion comprising polyethylene glycol. Nine fast-dissolving film formulations of LAN were prepared using the solvent casting process with polymers HPMC E15, PVP K30, and PVA. The thickness, weight variation, folding endurance, drug content, disintegration time, in-vitro drug release, and stability study of LAN films were evaluated as quality control tests. The folding endurance of all formulations was within the range of 100-150, with the exception of F5, F6, F7, and F9, which fell short of the required limits. Except for F5, F6, and F9, the disintegration time of all the formulations found in the limit. Each formulation's drug content ranged from 86.12 to 98.80 percent. In vitro drug release studies confirmed that formulation F3 is the most effective of the nine prepared formulations. The in-vitro drug release study of F3 demonstrated the highest percentage of drug release compared to other formulations. The F3 formulation was used for stability studies. According to stability studies, the formulation was found to be stable for three months. The results suggest that fast-dissolving LAN films with higher solubility could lead to enhanced bioavailability and a viable therapy for stomach ulcers.

Keywords:β cyclodextrin, Cross Povidone, Fast dissolvingfilms, Lanzoprazole,Solid dispersion, Ulcer.

INTRODUCTION

Recently, fast-dissolving drug delivery systems have begun to acquire popularity and acceptance as innovative drug delivery methods that attempt to improve the safety and efficacy of a

therapeutic molecule by putting it into a convenient dosage form for administration and achieving more patient compliance. The film is placed on the tongue's top or bottom[1]. This film instantly disintegrates when placed on the tongue, releasing the drug, which dissolves in the saliva. Certain drugs are absorbed from the mouth, throat, and esophagus as saliva travels to the stomach. In such instances, the drug's bioavailability is much greater than that of ordinary tablets[2].

For many acute and chronic disorders, significant efforts have been undertaken in recent years to produce dosage forms with increased patient compliance, enhanced therapeutic effectiveness, fewer side effects, and reduced dosage regimens with less toxicity[3]. Multiple drug delivery technologies with fast disintegration are developed and commercialised.[4-5]The section of oral drug administration has shifted from basic conventional films or capsules to modified-release films or capsules, and then to fast-dissolving films (FDFs). These innovative, patient-friendly, and more convenient films can be taken with or without water[6].

A new oral fast-dissolving dosage form, such as the fast-dissolving film, has been developed that combines the advantages of convenience and dosing without water. Oral fast dissolving film is a relatively recent dosage form in which hydrophilic polymers are used to create a thin film that rapidly dissolves on the tongue or in the buccal cavity[7]. Oral Fast dissolving film (FDF) is also known as oral strips, orodispersible films(ODF), and mouth dissolving films (MDF). When fast dissolving films are placed in the mouth, saliva immediately dissolves the dose form[8]. The saliva with the dissolved or scattered drug is subsequently swallowed, and the drug is absorbed as normal. Some drugs are absorbed from the mouth, pharynx, and esophagus as saliva travels down into the stomach, and this may result in an immediate commencement of action[9]. In such circumstances, the drug's bioavailability is much greater than that reported with normal tablets[10].

Solid dispersion is drug dispersed in a biologically inert matrix and it refers to a group of solid products consisting of at least two different components, generally hydrophobic drug and hydrophilic carrier[11]. The carrier can be either crystalline or amorphous. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug gets released as fine colloidal particles and as a result there is enhancement of solubility/dissolution rate of poorly water soluble drugs[12].

Peptic ulcers are caused by the production of stomach acid and pepsin (an enzyme). Patients with ulcers typically create more acid than individuals without ulcers[13]. In addition, the ulcer patient's

stomach or intestinal wall may lack sufficient natural defenses to resist the effects of acid and pepsin[14]. Researchers may not yet know all the causes of excessive acid production, but many believe that controlling acid production is the key to curing an ulcer. Peptic ulcer may also be caused by Helicobacter pylori, or H. pylori, and Nonsteroidal anti-inflammatory medicines (NSAIDs) such as aspirin and ibuprofen[15]. Hence the goal of the present study was to develop and evaluate lanzoprazole fast-dissolving films. Lansoprazole (LAN) is an inhibitor of the proton pump used to treat stomach ulcers. The BCS classifies lansoprazole as a drug of class II with limited water solubility. In order to improve the drug's solubility, we developed Lansoprazole solid dispersion comprising polyethylene glycol. Then nine fast-dissolving films of developed LAN solid dispersion were prepared using the solvent casting process with polymers HPMC E15, PVP K30, and PVA.

MATERIALS AND METHODS:

Lansoprazole was purchased from Alpa Laboratories Limited, Indore.PEG4000,HPMC E15 and Methanol were purchased from S.D. fine chemicals, Mumbai. PVP K30 was purchased from Qualigen, Mumbai. Aspartame, PVA and Glycerol were used of LOBA ltd.

Preparation of solid dispersions of Lansoprazole (SD)

Solid dispersions were produced by solvent evaporation using PEG4000 as a carrier in the amounts 1:1, 1:2, and 1:3. (Drug: Carrier). Methanol is chosen as the typical solvent for solid dispersion (Table 1). The relevant amount of carrier was dissolved in 20 ml of methanol, then LAN was added in portions while stirring continuously. Afterward, the solvent was eliminated by evaporation. The prepared solid dispersion was ground and passed through sieve No. 100 before being stored in desiccators over fused calcium chloride. A physical mixture of the medication and carrier containing the same proportions as the solid dispersion was also created[16-18].

Table 1: Composition of Various Solid Dispersions of drug

S. No.	Formulation code	Composition	Ratio
1.	SD1	LAN : PEG 4000	1 : 1
2.	SD2	LAN : PEG 4000	1 : 2
3.	SD3	LAN : PEG 4000	1 : 3

Evaluate for solid dispersion of drug

Physical mixture and solid dispersions equal to 10 mg of LAN were added to 10 ml of PBS pH 6.8 in a volumetric flask of 10 ml. 24 hours were spent shaking the volumetric flasks at 25°C in a temperature-controlled water bath (Shaking water bath). Samples containing undissolved solids suspended in the volumetric flask were filtered through 0.45m filters, diluted with PBS at pH 6.8, and examined at 284 nm by UV spectrophotometer[19].The drug content was determined by dissolving drug complex and solid dispersions equal to 50 mg LAN in 10 ml of methanol, filtering through 0.45m Whatman filter paper, and diluting the filtrate with 100 ml PBS (pH 6.8)[20].

100 mg equivalent solid dispersion of LAN was used to determined dissolution rate. At 5, 10, 15, 20, and 25 minutes, 5 ml aliquots were extracted and replaced with 5 ml of new dissolving media. After filtration and dilution, materials were examined using a UV-visible spectrophotometer at 284 nm against a blank[21-22].

Formulation ofLansoprazole Fast Dissolving Films

In distillated water, a polymer solution (HPMC E15) was made. Composition of polymer solution was created according to formula in table 2. The recommended therapeutic dose of lansoprazole (LAN) is 30 mg. In the polymeric solution, the optimized LAN:PEG 4000 solid dispersion (SD3- 1:3) with 84 mg of LAN equivalent weight was dissolved. After the drug was completely dissolved, glycerol (plasticizer) was added and stirred to create a homogenous solution. Aspartame was then added and mixed to create a uniform mixture. The solution was poured into a mold and maintained in a 60°C hot air oven for twenty-four hours. The resulting film was sliced into 2.5 x 2.5 cm square strips. For future research, the prepared square thin film strips were preserved in desiccators[23-24]. The components of LAN oral films are listed in Table 2.

Table 2:Composition of FDFs of Lansoprazole SD

Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lansoprazole SD (SD3) (equivalent to 30mg drug) (mg)	84	84	84	84	84	84	84	84	84
HPMC E15 (mg)	120	240	360	80	120	270	80	120	270
PVP K30 (mg)	-	-	-	40	120	90	-	-	-
PVA (mg)	-	-	-	-	-	-	40	120	90
Aspartame (mg)	5	5	5	5	5	5	5	5	5
Glycerol (ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Distilled Water q.s. (ml)	10	10	10	10	10	10	10	10	10

Evaluation of LansoprazoleFDFs

Fast dissolving oral films were weighed on a digital balance, and the average weight was determined for each film. By using a micrometer screw gauge, the thickness of the film was measured at five different places; an average of 3 values was calculated. A strip of 2.5 cm × 2.5 cm was subjected to folding endurance by folding the film at the same place repeatedly several times until a visible crack was observed, and the values were reported[26].The prepared fast-dissolving film was dissolved in 50ml PBS pH 6.8 and filtered through Whatman filter paper. After suitable dilutions, the concentration of the drug was determined by measuring the absorbance at 284nm.Disintegration test was performed using 6.25 cm^2 film. The time required by the film, when no traces of film remain above the gauze was noted[27-28].

In-vitro Dissolution study was carried out using USP type II (basket type) apparatus with PBS pH 6.8 as a dissolution medium. The temperature was maintained at 37±0.5^{0}C with 50 rotations per minute. 5ml of aliquots were withdrawn at different time intervals, and the same amount of fresh dissolution medium was replaced to maintain sink condition. The dissolution samples, after filtration through 0.45-mm filters were analyzed for drug content at λ max 284 nm wavelength using UV-spectrophotometer. The cumulative percentage drug release was calculated and reported[29].The stability study of the formulated fast-dissolving films was carried out under different environmental conditions of 2-8°C (45% RH), 25-30°C (60% RH), and 45-50°C (75% RH) for 90 days. The films were characterized by drug content during the stability study period[31].

RESULTS AND DISCUSSION

The solubility of solid dispersion SD1 to SD3 was found to be in the range of 1.45 mg/ml to 3.91 mg/ml. Drug content of the solid dispersion SD1 to SD3 was found to be in the range of 97.24% to 99.31% (Table 3).

Table 3: Drug content and Solubility of SD and DC of Lansoprazole

Formulation Batch	Amount of Drug Soluble (mg/ml)	Drug Content (%)
SD1	1.45	97.24
SD2	1.82	98.96
SD3	3.91	99.31

From the results of cumulative drug release study it can be seen that more than 50 % of drug was released in less than 10 mins and more than 90 % drug is released in 20 mins. Formulations SD1 & SD2 showed drug release of 97.65 % and 98.13 % at the end of 20 mins. Formulation SD3 showed drug release of 99.17 % at the end of 15 mins. Drug release from physical mixture (PM) was only 52.76% in 20mins (Figure 2).From the data of % CDR, it is note that as the polymer changes the drug release profile also changes. From the results we concluded that the batch SD3 having PEG4000 (1:3) as polymer showed better release profile as compared to other batches and selected for formulation of fast dissolving tablets.

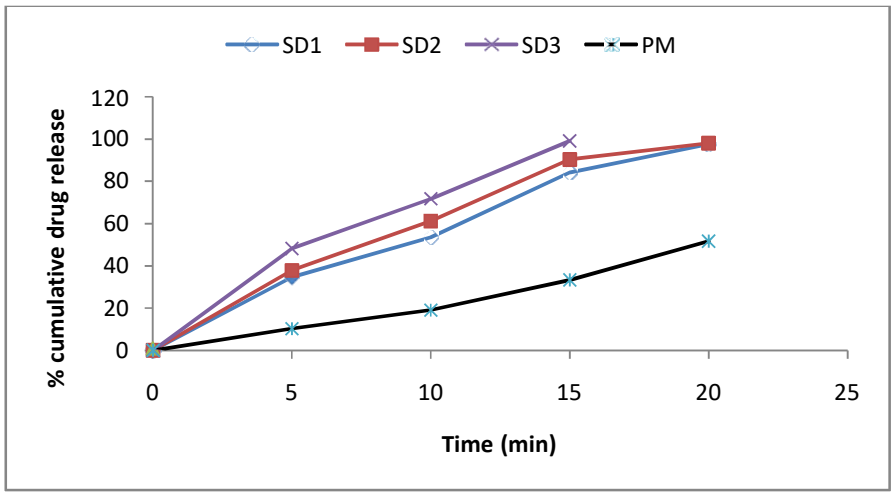

Figure2: Comparison of *in vitro* drug release from SD and PM of Lansoprazole

Evaluation of FDFs of Lansoprazole SD (SD3)

The film weight was found to be in the range of 35mg to 40mg which ensured uniform distribution of the drug in all the formulations.The thickness of F1 to F9 was found to be 98-110µm. The folding endurance value of F1 to F9 was found to be 48-110. The percentage of drug content of F3 was found to be 98.80% and was considered as the best formulation compared to the other formulation. The formulations showed the percentage of drug content 86.12-98.80% (Table 4). The disintegration time of F3 was found to be 10 seconds, which took less time than all other formulations (F1-F9).

Table 4: Weight variation of fast dissolving films of LAN (±SD, n=3)

Formulation	Weight (mg)	Thickness (µm)	Folding endurance	% Drug content
F1	35.25±1.2	98±1.5	106±2	86.12±02.98
F2	38.32±3.2	100±3.2	101±4	90.43±1.86

F3	35.12±2.6	102±2.6	110±2	98.80±0.66
F4	36.45±1.4	101±2.4	102±4	94.25±0.94
F5	36.90±3.2	105±4.1	62±3	91.44±1.75
F6	39.08±2.1	109±2.1	54±4	93.17±1.12
F7	40.0±2.5	99±1.6	102±2	93.52±1.24
F8	36.63±3.8	106±3.8	63±1	97.26±1.08
F9	40.05±1.4	110±1.4	48±6	89.50±2.56

The drug release was found to be in the following order: F3 > F9 > F8 > F1 > F4 > F7 > F5 > F6. Among the nine formulations (F1 to F9) prepared, formulation F3, was found to be the best formulations in drug release (Figure 3& 4).

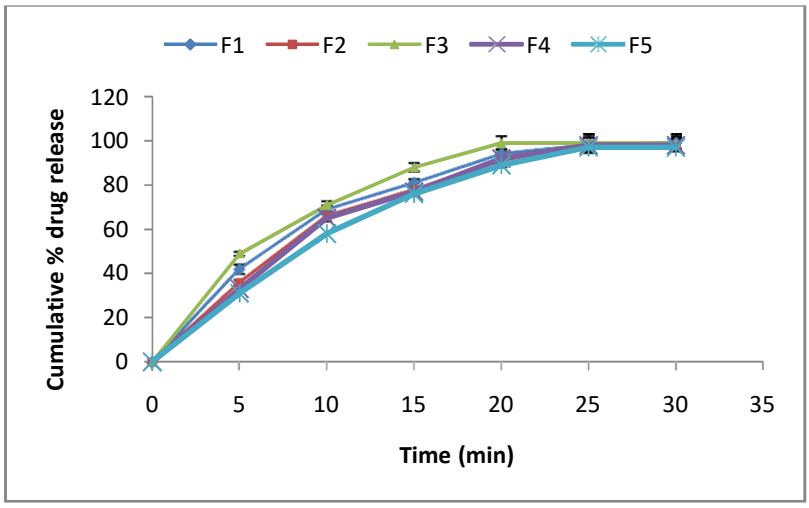

Figure 3:Cumulative%drug release from fast dissolving films of LAN (F1-F5)

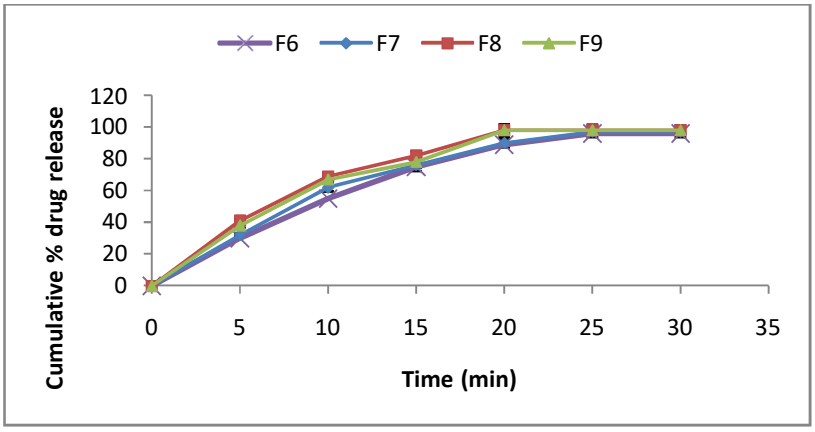

Figure 4:Cumulative%drug release from fast dissolving films of LAN (F6-F9)

The stability study for the prepared film was carried out for 90 days at different temperature and humidity conditions. Fast-dissolving film (F3) was found to be physically and chemically stable as they showed no significant change in terms of physical characteristics and drug content at a lower temperature and room temperature. However, when stored at 45-50°C for 90 days, films became brittle (Table 5).

Table 5:Stability study of fast dissolving films (F3) of LAN (±SD, n=3)

S. No.	Parameter	Initial	1 month	2 months	3 months
1	Thickness	99±1.8	99±1.8	99±1.6	99±1.5
2	Weight variation	35.12±2.6	35.12±2.6	35.12±2.6	35.62±0.8
3	Folding endurance	110±2	110±2	110±4	106±4
4	Disintegration time (sec)	10±1.2	10±1.2	11±2.0	14±2.4
5	Drug content (%)	99.80±0.66	99.76±1.06	99.06±1.14	98.96±1.58

CONCLUSION

Present research proved the feasibility of developing a fast-dissolving film of a proton pump inhibitor drug. PEG4000 solid dispersions were prepared to increase drug solubility in water. Several different polymers were used in a solvent casting method to produce a quick dissolving film for this technology. Disintegration was determined to be adequate in 10 seconds, and in-vitro lansoprazole release was reported to be 99±2.8% within 20 minutes. The results of this research show that the fast-dissolving films prepared for this study are effective in treating stomach ulcer symptoms by delivering Lansoprazole rapidly into the body.

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