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FORMULATION AND EVALUATION OF SUBLINGUAL TABLETS CONTAINING ESOMEPRAZOLE SODIUM

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ABSTRACT

The objective of the present research work was to develop and optimize a sublingual tablet of Esomeprazole sodium which is indicated for the treatment of gastro oesophageal reflux disease, by direct compression method. The tablets were prepared using four different superdisintegrants such as sodium starch glycolate, cross carmellose sodium, crosspovidone and Indion 414. The prepared tablets were evaluated for their physical characteristics and *in vitro* drug release properties. *In vitro* release study was carried out using USP dissolution apparatus 2. The results revealed that the batch of tablets (F-13) formulated containing Indion 414 provides short wetting time of 8.2 seconds and in vitro disintegration time of 18.7 seconds, which facilitates its faster disintegration and drug content of 99.54%, and *in-vitro* drug release was found to be in formulation F-13 i.e. 99.86% within 120 seconds. From the above results, it indicate that Formulation F-13 emerged as the overall best formulation based on drug release characteristics with pH 6.8 phosphate buffer as dissolution medium. Stability studies were carried out which indicated that the selected formulation F-13 was found to be stable.

KEYWORDS: Sublingual tablet, Esomeprazole sodium, Gastro oesophageal reflux disease, Superdisintegrant, Indion 414.

1. INTRODUCTION

Gastroesophageal reflux disease (GERD) is a spectrum of disease that can be defined as the symptoms and/or signs of oesophageal or adjacent organ injury secondary to the reflux of gastric contents into the oesophagus or beyond, into the oral cavity or airways. Injury is

defined based on symptoms or organ damage resulting in esophagitis, laryngeal inflammation, or acute and/or chronic pulmonary injury. GERD encompasses a heterogeneous group of patients with differences in sensitivity to oesophageal acid exposure, perception of pain, and physiological tissue involvement. Though it is not usually life-threatening, GERD can have a major effect on patient's well-being and quality of life.[1-2] Esomeprazole, the S-isomer of omeprazole is a new pharmacological entity which have the superior acid control due to an advantageous metabolism compared with racemate omeprazole, leading to improved bioavailability and enhanced delivery of the drug to the gastric proton pump.[3] It has been well proven as an effective agent in the treatment of gastro-esophagitis reflux disease, (reflux esophagitis and non-erosive reflux disease), NSAID-induced gastric-intestinal symptoms and ulcers, *Helicobacter pylori* infection and Zollinger-Ellison syndrome. Esomeprazole has a good tolerability profile and a low potential for drug interaction.[4] Among the various routes of drug delivery, oral route is the most suitable and most widely accepted one by the patients for the delivery of the therapeutically active drugs. But, after oral drug administration many drugs are subjected to presystemic clearance in liver, which often leads to a lack of correlation between membrane permeability, absorption and bioavailability.[5-8] Within the oral route, the oral cavity is an attractive site for drug delivery due to ease of administration and avoids possible drug degradation in the gastrointestinal tract as well as first pass hepatic metabolism.[9] Sublingual literally meaning is "under the tongue", administrating substance via mouth in such a way that the substance is rapidly absorbed via blood vessels under tongue. In terms of permeability, sublingual area of oral cavity is more permeable than buccal area which is in turn is more permeable than palatal area.[10] Systemic drug delivery through the sublingual route provides immediate onset of pharmacological effect. Dysphagia (difficulty in swallowing) is a common problem of all age groups, especially elderly, children, and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid intake/diets have difficulties in swallowing these dosage forms.[11,12] In terms of permeability, the sublingual area of the oral cavity is more permeable than the buccal (cheek) area, which in turn is more permeable than the palatal (roof of the mouth) area. The differences in permeability are generally based on the relative thickness, the blood supply, and degree of keratinization of these membranes. In addition to the differences in the permeability of the various mucous membranes, the extent of drug delivery is also affected by the physicochemical properties of the drug to be delivered.[13]

2. MATERIALS AND METHODS

2.1. Materials

Esomeprazole sodium was obtained as a gift sample from RMS Research labs (P) ltd, Hyderabad, India. Indion 414 was received as a gift sample from Ion exchange India ltd, Mumbai and microcrystalline cellulose (Avicel®PH-102) was received as a gift sample from Sun Pharmaceutical Industries Ltd., Dadra. Sodium saccharin was obtained as a gift sample from SD fine chemicals Mumbai. All other excipients and chemicals were of analytical grade.

2.2 Formulation and preparation of Sublingual tablets by direct compression method

Sublingual tablets were prepared by direct compression method. All the ingredients were screened through sieve no.100. Esomeprazole sodium was mixed manually with sodium starch glycolate (SSG), crosscarmellose sodium (CCS), crosspovidone, Indion 414, sodium saccharin, mannitol and microcrystalline cellulose PH 101 (MCC PH 101) as diluent for 10 min. The blend was mixed with magnesium stearate and talc for 3-5 min and then powder blends of batches F1-F13 were evaluated for powder characteristics like bulk density, tapped density and angle of repose. Then the powder blend were compressed into tablets by the direct compression method using 8 mm flat faced punches using rotary tablet-punching machine. The compositions of batches F1-F13 are shown in **Table 1**.

Table 1: Composition of Esomeprazole sublingual tablet

Sr. No.	API	SSG	CCS	Crosspovidone	Indion 414	Sodium saccharine	Mannitol	MCC PH 101	Magnesium stearate	Talc
F1	20	-	-	-	-	1	90	81	4	4
F2	20	4	-	-	-	1	90	77	4	4
F3	20	6	-	-	-	1	90	75	4	4
F4	20	8	-	-	-	1	90	73	4	4
F5	20	-	4	-	-	1	90	77	4	4
F6	20	-	6	-	-	1	90	75	4	4
F7	20	-	8	-	-	1	90	73	4	4
F8	20	-	-	4	-	1	90	77	4	4
F9	20	-	-	6	-	1	90	75	4	4
F10	20	-	-	8	-	1	90	73	4	4
F11	20	-	-	-	1	1	90	80	4	4
F12	20	-	-	-	2	1	90	79	4	4
F13	20	-	-	-	4	1	90	77	4	4

SSG- Sodium starch glycolate, CCS- Cross carmellose sodium, MCC PH 101- Microcrystalline cellulose PH 101.

Note :-(Each tablet weighs 200mg) (All the quantities are expressed in mg)

2.3 Compatibility Study

2.3.1 Drug Excipient Compatibility Study[14]

The excipients were selected on the basis of preformulation study of drugs. All the excipients selected are listed in GRAS and IIG. The compatibility study of the drugs: excipients in physical mixture (1:1) were checked out using the Shimadzu FTIR spectrophotometer. Sample compartment was purged with nitrogen gas before runs, and filled with dry desiccant to absorb any moisture present. The sample pellets were prepared by making an approximately 10-15% of system with dry KBr (IR grade). Powders were triturated in a small size mortar and pestle until the powder mixture was fine and uniform. Pure KBr powder was used as background, and for baseline correction. Samples were placed in a sample holder. Afterwards, the sample was transferred to sample compartment and scanned in the region of 4000-400 cm^{-1} using a Shimadzu spectrophotometer.

2.4 Evaluation of Tablet[15,16]

2.4.1 Weight Variation

20 tablets were taken at random for the test and were weighed, individually and the average weight was calculated. The % deviation of each tablet from the average weight was calculated.

2.4.2. Hardness

The hardness of the tablets were measured using a simple Monsanto hardness tester. In this, a tablet was placed between the plungers, and was tightened from one end, and pressure required to break the tablet diametrically was measured.

2.4.3 Friability

The test tablets were weighed and placed in a Roche Friabilator test apparatus. The friability was determined as the percentage loss in weight of the tablets

% Friability = 1 - (wt. of tablets after test/ wt. of tablets before test) x 100

2.4.4 Dimensions

The dimensions of tablets were measured using the vernier caliper scale. Tablet thickness was controlled within a ± 5% variation of the mean value.

2.4.5 Disintegration time (in vitro)

The test was carried out using a tablet disintegration apparatus (Cintex Ind. Corp., Mumbai, India). Distilled water was used as the disintegrating medium at 24 ± 0.2°C. The time required to obtain complete disintegration of all the tablets was noted.

2.4.6 In Vitro Drug release Study

The *in vitro* release of Esomeprazole sodium from the formulated tablet was carried out in USP dissolution test apparatus II using 900 mL of dissolution medium maintained at 37.0 ± 0.5°C and a stirring rate of 50 rpm. Each formulation was tested individually in 900 mL phosphate buffer (pH 6.8). At every 30 seconds interval, samples of 5 mL were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the amount of drug released in each sample was determined spectrophotometrically.

2.4.7 Stability Studies[17,18]

The tablets were stored at 40 ± 2 ºC/75 ± 5 % RH for duration of one month. After an interval of fifteen days and thirty days samples were withdrawn and tested for various physical tests and drug release study.

2.4.8 Wetting time[19]

The tablet was placed at the center of two layers of absorbent paper fitted into a petridish. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch. The evaluation parameters of batches F1-F13 are shown in Table 2.

2.4.9 Drug content

Tablets (n = 5) were weighed individually, and the drug was extracted in phosphate buffer (pH 6.8), and the solution was filtered by Whatman filter paper. Absorbance was measured after suitable dilution using a Shimadzu UV-1800 UV/ Vis double-beam spectrophotometer.

3. RESULTS AND DISCUSSION

3.1 COMPATIBILITY STUDY

FTIR STUDY

Esomeprazole sodium exhibits a peak due to N–H stretching at 3429.01 cm^{-1}, S=O stretching at 1076.98 cm^{-1}, -C-O stretching at 1153.20 and -C=N stretching at 1611.25 cm^{-1}. It was observed that there were no changes in these main peaks in the FTIR spectra of a mixture of drug and excipients. Hence, it was concluded that no physical or chemical interactions of Esomeprazole sodium with excipients. FTIR spectra of a mixture of drug and excipients are shown in **Figure1-11**.

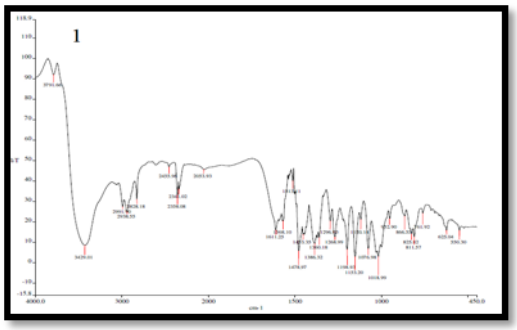


Fig. 1.

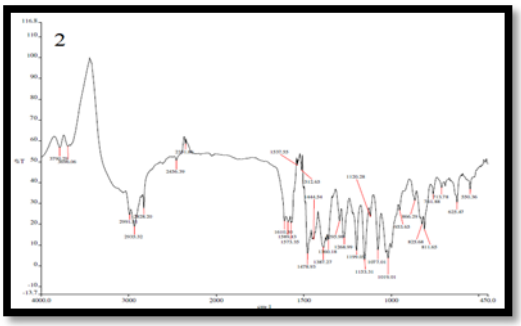


Fig. 2.

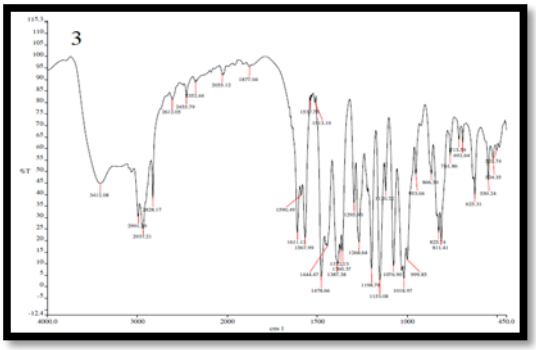
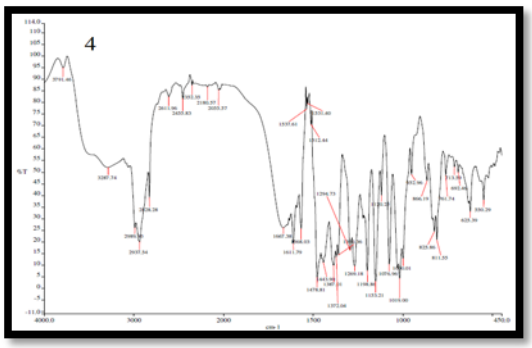


Fig. 3.



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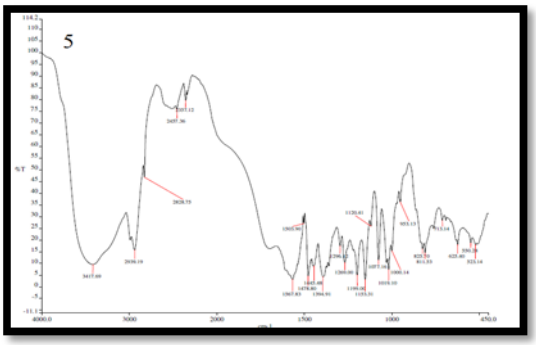
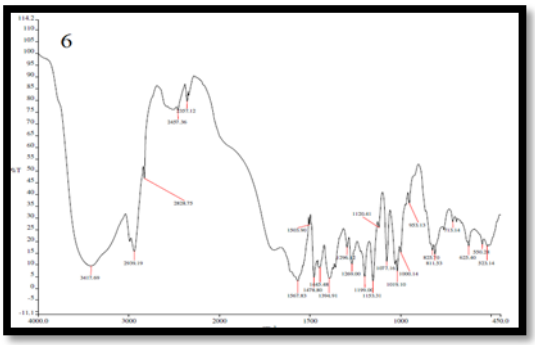


Fig. 5.



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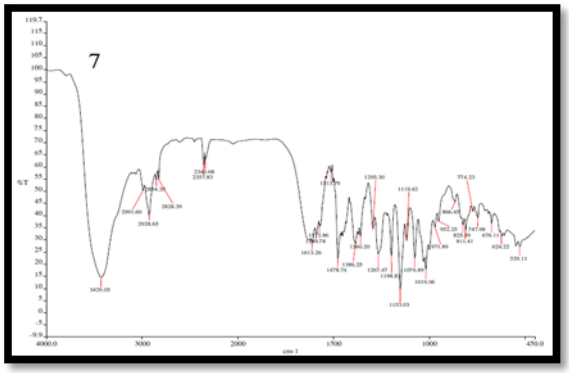


Fig.7.

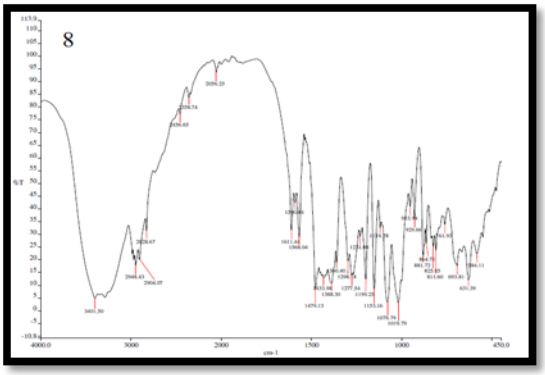


Fig. 8.

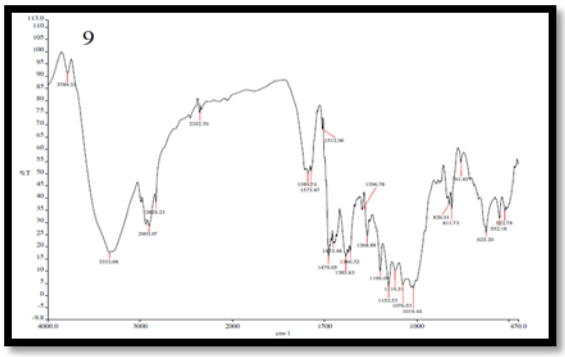


Fig. 9.

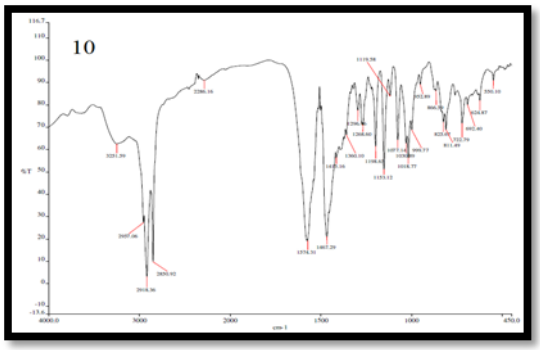


Fig. 10.

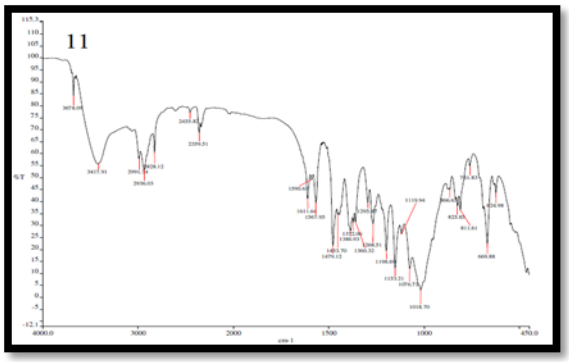


Fig. 11

Fig. 1; Fig. 11: FTIR spectra of

1. Drug
2. Drug + Sodium Starch Glycolate
3. Drug + Crosscarmellose Sodium
4. Drug+ Crosprovidone
5. Drug+ Indion414
6. Drug+ Kyrone 314

7. Drug + Sod. Saccharine
8. Drug + Mannitol
9. Drug + Avicel PH 102
10. Drug+ Magnesium Stearate
11. Drug +Talc

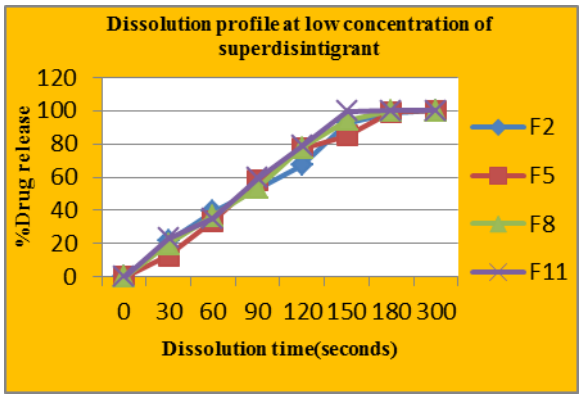
3.2 Evaluation of sublingual tablets

The results of powder characteristics of blends of all batches showed good flow properties and compressibility. The prepared tablets were evaluated for weight variation, hardness, thickness, friability, drug content, wetting time, in vitro disintegration time, and in vitro dissolution. It was observed that all the tablets formulation passed the test for weight variation, as the percentage of weight variation was within the pharmacopeial limits. The prepared tablets in all formulations possessed good mechanical strength with sufficient hardness in the range of 4.1 to 4.9 kg/cm^2. The tablets mean thickness was almost uniform, between 3.03 to 3.11 mm in all formulations. Friability varied between 0.21% and 0.72% which is less than 1% were an indication of good mechanical resistance of tablets. The drug content in all formulations was highly uniform and in the range of 98.13-100.53%. Wetting time was found to be in the range of 8.2-114.2 sec. It was observed that formulation F13, containing 8% Indion 414 as super-disintegrant showed faster disintegration rate as compared with other formulations. The results of the evaluation parameters of the sublingual tablets are depicted in Table 4. Batch F13 showed the lowest disintegration time and wetting time, hence it was considered an optimized batch. *In vitro* drug release of batch F13 was 99.86 % in 2 min.

Table 2: Evaluation Parameters of Batches F1 to F13

Formulations	Diameter (mm) (n=5)	Thickness (mm) (n=5)	Hardness (kg/cm^2) (n=5)	Friability (%)	Disintegration time (Sec) (n=3)	Weight uniformity (n=20)	Wetting time (Sec)	Drug content (%)
F1	8.04± 0.056	3.11±0.14	4.8 ± 0.27	0.37	131 ± 1	199.2 ± 2.43	114.2± 3.76	99.45 ± 0.02
F2	8.03± 0.056	3.03±0.18	4.7 ± 0.27	0.29	80.7 ± 1.52	199.84 ± 1.89	74±2.73	100.53 0.523
F3	8.03±0	3.03±0.9	4.9 ± 0.22	0.45	54.7 ± 3	199.78 ± 1.91	45.8± 2.68	99.44 ± 0.026
F4	8.03±0	3.03±0.74	4.5 ± 0.35	0.36	31.7 ± 1.52	199.63 ± 2.03	28.2± 1.48	99.436 ± 0.030
F5	8.03±0	3.03±1.37	4.3 ± 0.27	0.67	102.3 ± 1.52	200.1 ± 1.85	96.6± 2.60	98.84 ±0.055

F6	8.03±0	3.08±1.16	4.8 ± 0.27	0.72	71.3 ± 1.52	200.68 ± 1.81	62±1.58	98.13 ± 0.041
F7	8.03±0	3.08±1.38	4.3 ± 0.44	0.32	48 ± 2	200.47 ± 1.68	44.6± 1.67	99.23 ± 0.032
F8	8.04± 0.056	3.08±0.1	4.6 ± 0.41	0.34	89.7 ± 2.51	199.68 ± 1.86	87.2± 1.30	98.69 ± 0.40
F9	8.04± 0.056	3.08±0.14	4.7 ± 0.44	0.51	65 ± 1	200.31 ± 1.54	52.8± 2.28	99.433 ± 0.025
F10	8.03± 0.056	3.08±0.18	4.8 ± 0.44	0.30	44.3± 2.51	199.84 ± 2.38	32±1.58	99.556 ± 0.015
F11	8.03±0	3.08±0.9	4.1 ± 0.41	0.57	79 ± 2.64	200.68 ± 1.83	72.4± 2.07	99.94 ± 0.047
F12	8.03± 0.056	3.08±0.18	4.9 ± 0.22	0.29	33 ± 2.64	200.31 ± 1.65	34.2± 2.48	99.55 ± 0.017
F13	8.03±0	3.08±0.9	4.3 ± 0.57	0.21	18.7 ± 1.52	199.94 ± 2.50	8.2± 1.30	99.543 ± 0.011



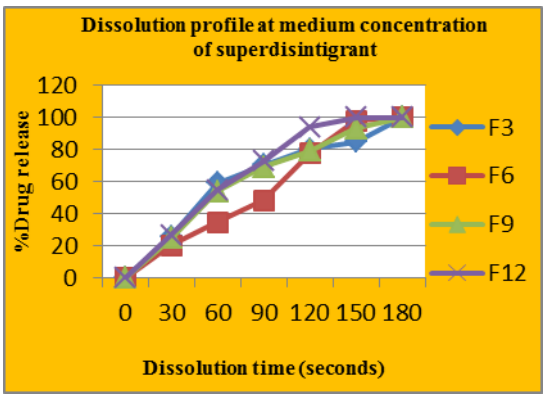


Fig. 12: Dissolution profile at low conc. of superdisintigrant F2, F5, F8, F11

Fig. 13: Dissolution profile at medium conc. of superdisintigrant F3, F6, F9, F12.

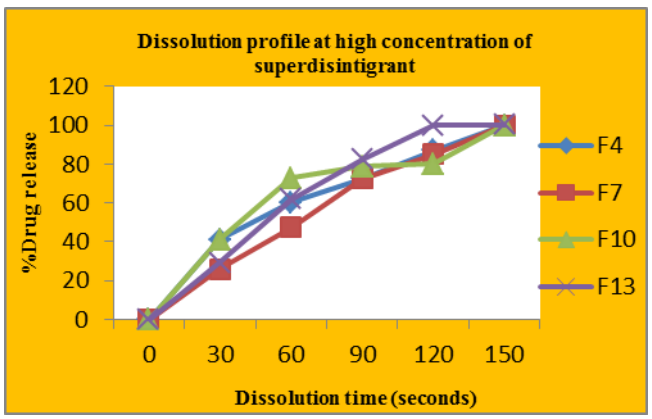
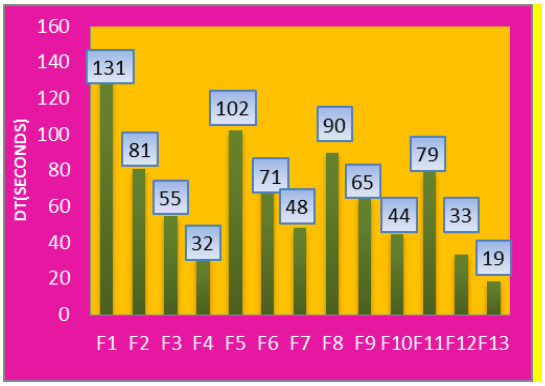


Fig. 14: Dissolution profile at high conc. of superdisintigrant F4, F7, F10, F13.



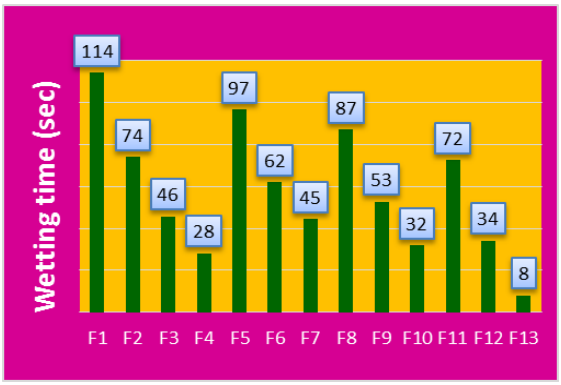


Fig. 15: Disintegration time of batches F1 to F13. **Fig. 16: Wetting time of batches F1 to F13.**

3.3 Stability data of optimized formulation

Table 3: Stability data of optimized formulation.

Condition	Weight uniformity	Drug content
Initial	199.94 ± 2.50	99.543 ± 0.011
15 Days		
40°C ± 2°C/75% RH ± 5% RH	199.89 ± 1.82	99.45 ± 0.02
30 Days		
40°C ± 2°C/75% RH ± 5% RH	199.84 ± 1.87	99.44 ± 0.026

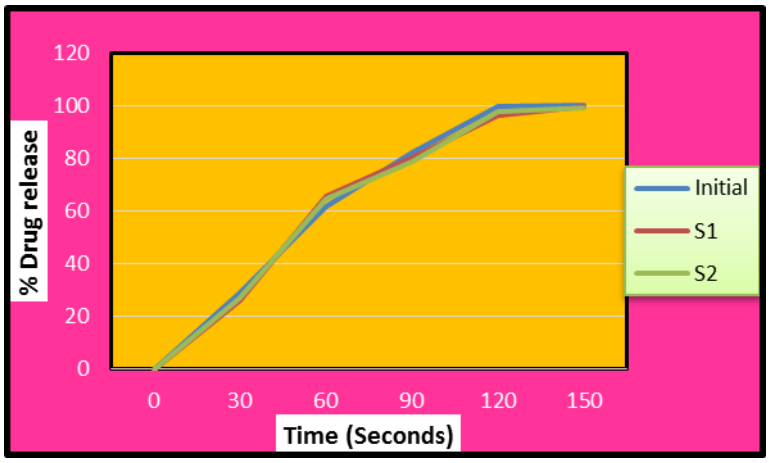


Fig. 17: *In Vitro* Drug release of Esomeprazole sodium from sublingual tablet after stability study

Form the weight uniformity, drug content and dissolution profile of sublingual tablets it was observed that there was no major change either in weight uniformity, drug content and dissolution profile after stability studies. It indicates that, these formulations are able to retain their stability.

CONCLUSION

Sublingual tablets of Esomeprazole sodium were prepared by direct compression method. It was shown that with the developed formulations, the disintegration time and release properties of sublingual tablets can be controlled by changing the disintegrant type and concentration. The formulation F13 consist of 4 mg of Indion 414 was selected as the best formulation. Various physicochemical parameters tested for this formulation showed good results.

It was concluded that development of sublingual drug delivery of Esomeprazole sodium tablet was one of the alternative route of administration to avoid first-pass effect. This finding suggested that the Esomeprazole sodium tablets have a strong potential for use as a sublingual delivery system.

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REFERENCES

1. Katz PO. Gastroesophageal Reflux Disease. Journal of the American Geriatrics Society, 1998; 46: 1558–65.
2. Kahrila PJ. Diagnosis of symptomatic gastroesophageal reflux disease. The American Journal of Gastroenterology, 2003; 98: S15-23.
3. Tonini M, Vigneri S, Savarino V, Scarpignato C. Clinical pharmacology and safety profile of esomeprazole, the first enantiomeracally pure proton pump inhibitor. Dig. Liver Dis., 2002; 33: 600–06.
4. Saccar CL. The pharmacology of esomeprazole and its role in gastric acid related diseases. USA Expert Opin. Drug Metab. Toxicol, 2009; 5: 1113-24.
5. El-Samaligy MS, Yahia SA, Basalious EB. Formulation and evaluation of diclofenac sodium buccoadhesive discs. International Journal of Pharmaceutics, 2004; 286: 27-39.
6. Rossi S, Sandri G, Caramella CM. Buccal drug delivery: A challenge already won. Drug Discovery Today: Technologies, 2005; 2(1): 59-65.
7. Kadam PB, Dias RJ, Mali KK, Havaldar VD, Mahajan NS. Formulation and evaluation of buccoadhesive tablets of Atenolol. J Pharm Res., 2008; 1(2): 193-99.

8. Nafee NA, Ismail FA, Boraie NA. Mucoadhesive Delivery Systems. I. Evaluation of Mucoadhesive Polymers for Buccal Tablet Formulation. Drug Dev Ind Pharm, 2004; 30(9): 985- 93.
9. El-Samaligy MS, Afifi NN, Mahmoud EA. Increasing bioavailability of silymarin using a buccal liposomal delivery system: Preparation and experimental design investigation. International Journal of Pharmaceutics, 2006; 308: 140-48.
10. Patel NK. et al. An Overview on: Sublingual Route for Systemic Drug Delivery. International Journal of Research in Pharmaceutical and Biomedical Sciences, 2012; 3(2): 913-23.
11. Ishikawa T, Koizumi N, Mukai B. Pharmacokinetics of acetaminophen from rapidly disintegrating compressed tablet prepared using microcrystalline cellulose (PH-M-06) and spherical sugar granules. Chem Pharm Bull, 2001; 49: 230-32.
12. Price TM, Blauer KL, Hansen M, Stanczyk F, Lobo R, Bates GW. Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17 beta-estradiol. Obstet Gynecol, 1997; 89: 340-45.
13. Kurosaki Y, Takatori T, Nishimura H, Nakayama T, Kimura T. Regional variation in oral mucosal drug absorption permeability and degree of keratinization in hamster oral cavity. Pharm Res., 1991; 8: 1297-1301,
14. Lachman L, Liberman HA, Kanig JL. The Theory and Practice of industrial Pharmacy. Varghese Publishing House, Bombay, 1987; 3: 297-300.
15. Indian Pharmacopeia, Government of India Ministry of Health and Family Welfare, Published by: The Controller of Publications. Delhi, 1996; 2: A-82-84.
16. Roukville A. United States Pharmacopoeia XXIV NF 19: United States Pharmacopoeial Convention, 2000; 1913-14.
17. Cartensen J, ICH Guidelines, In: Drug Stability Principles and Practices. New York: Marcel Dekker, Inc., 1995; 68: 541-46.
18. Kanvinde SA, Kulkarni MS. Stability of oral solid dosage forms- A Global Perspective. Pharma Times, 2005; 37: 9-16.
19. Bayrak Z, Tas C, Tasdemir U, Erol H, Ozkan CK, Savaser A, Ozkan Y. Formulation of zolmitriptan sublingual tablets prepared by direct compression with different polymers: In vitro and in vivo evaluation. Eur J Pharm Biopharm, 2011; 78: 499- 505.