International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Formulation or Evaluation of Floating Bilayer Tablet of Aceclofenac and Esomeprazole

Yogesh Kaushal[1], Dr Ravinesh Mishra[2], Dr. Bhartendu Sharma[3]

[1]Research scholar, school of pharmacy and emerging science, Baddi University of Emerging Sciences and Technology, Baddi , Himachal Pradesh
[2]Dean of Pharmacy, School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences and Technology, Baddi, Solan, H.P.,
[3]HOD of Pharmacy, School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences and Technology, Baddi, Solan, H.P.,

ABSTRACT
The development of bilayer floating tablets containing esomeprazole and aceclofenac was the objective of this study. OTC analgesics, like NSAIDs, are extensively used, but they are frequently abused and may be harmful, and users are often unaware of the possibility of adverse effects. It consists of an instant release aceclofenac layer and a floating sustained release esomeprazole layer manufactured using the wet granulation method. Aceclofenac was included into five immediate release layer formulations (F1–F5) made with sodium starch glycolate super disintegrants. To create five formulations of sustained release layer containing Esomeprazole (F1-F5), synthetic release retarding polymers (HPMC E15) were combined with other ingredients. The immediate release formulation (F3) released 97 % of the Aceclofenac in 1 hours, and the sustained release formulation (F5) released 96 % of the esomeprazole in 10 hours. There was an inverse relationship between the amount of polymer present and the amount of drug released. There were no chemical interactions between the drug and the polymers used, according to an FTIR analysis. 10% to 20 percent of patients who take nonsteroidal anti-inflammatory medicines (NSAIDs) develop stomach ulcers. This bilayer floating tablet containing aceclofenac and esomeprazole is useful for managing pain and inflammation in addition to NSAID-induced ulcer.

Keywords Aceclofenac, Esomeprazole, HPMC, GRDDS, Drug delivery system, Floating, Gastric residence time.

Introduction

Bilayer tablet is the newer for the effective development of controlled release formulations and better than the conventionally utilized dosage forms. A bilayer tablet is used for the sequential release of two medications in combination. It also able to separate two types of incompatible compounds, as well as producing sustained release tablets with one layer providing immediate release as the initial dose and second serving as the maintenance dose. In certain circumstances, bilayered tablets include two sustained release layers of different drugs. Colors were utilized to identify the two different drugs or layer [1]. Bilayer tablets include two layers: one for immediate release and the other for sustained release. The immediate release layer comprises super disintegrates, which speed up the rate of drug release and provide a rapid commencement of effect (loading dose). On the other hand, by employing

different polymers as release retardants, the sustained release (maintenance dose) layer releases the medication continuously over an extended period of time. [2, 3]

Gastro retentive drug delivery systems (GRDDS) are those that hold dosage forms in the stomach . By constantly releasing the medication for an extended period prior to it reaching its absorption site, GRDDS improves regulated drug delivery and the absorption window while guaranteeing the drug's optimal bioavailability [4]**.**For localized action in the upper portion of the small intestine, such as the treatment of peptic ulcers, a longer gastric retention period in the stomach may be beneficial.[5]

Advantages of gastroretentive drug delivery system

- In compared to non-gastroretentive drug delivery, the gastroretentive drug delivery method may significantly improve the bioavailability of the therapeutic drugs, particularly those that undergo metabolism in the upper GIT.[6]
- Useful for drugs with shorter half life by sustained drug delivery.
- Increase patient compliance by lowering the frequency of doses.
- Reduced variation in drug concentration allows for increased selectivity in the receptor activation.
- The hydrodynamically balanced system (HBS) concept may be applied to any medication or class of medications. [7]
- The hydrodynamically balanced system (HBS) formulations are not limited to medications, which are mostly absorbed through the stomach. Since it has been shown that they are similarly effective with medications absorbed from the colon, such as chlorpheniramine maleate.
- The HBS are beneficial for drugs that are absorbed by the stomach, such as ferrous salts, as well as drugs that have a local effect in stomach and Antacids are commonly used to treat peptic ulcer disease.
- Gastric retention will give benefits such as medication administration with narrow absorption windows in small intestine. [8]
- Reduced variation in drug concentration allows for increased selectivity in the receptor activation.
- Slow drug release into the body reduces counter-activity, resulting in improved drug efficiency.
- The retention of the medication in GRDF in the stomach reduces the quantity of drug that enters the colon and so inhibits drug breakdown in the colon. [9]

Aceclofenac [10]

Aceclofenac is a phenyl acetic acid derivative that is taken orally and acts on many inflammatory mediators. The anti-inflammatory effect of aceclofenac is greater than that of traditional NSAIDs.The mechanism of action of aceclofenac is to inhibit the body's cyclooxygenase enzyme. Cyclo-oxygenase plays a role in the synthesis of prostaglandins, which are bodily substances that induce inflammation, pain, and swelling.

IUPAC name

2-[2-[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxyacetic acid

Chemical formula

C16H13Cl2NO4

Molecular weight
354.18 g/mol

Melting point
149-153^{O}C

Description
Aceclofenac is a white, odourless crystalline powder

Solubility
Soluble in alcohol, freely soluble in acetone, practically insoluble in water.

pka value
4.7

Storage
In an air tight container, protected from light

Pharmacokinetics data of aceclofenac

Table 1

Oral availability	100%
Bound in plasma	99%
Urinary excretion	70-80%
Volume of distribution	25 -30 L/kg
Half life 3-4 hrs	3-4 hrs

ESOMEPRAZOLE [11]
Molecular Formula:
$C_{34}H_{36}MgN_6O_6S_2$
Molecular Weight: 345.417 g/mol
Solubility:

- Partially soluble in acetone
- Easily soluble in methanol.
- Slightly soluble in chilled water, hot water.

Mechanism of Action:
Esomeprazole is a prodrug, like other PPIs, that gets converted to its active form (sulfenamide) in an acidic environment. The prodrug's active form forms a covalent bond with the stomach lumen's parietal cell-based H+/K+ ATPase pumps. Acid secretion pathway ends in the involvement of H+/K+ ATPase pumps. This bond prevents any further release of hydrogen ions irreversibly. The inhibition of acid generation lasts for around eighteen hours, or until new H+/K+ ATPase pumps regenerate.

Pharmacokinetics:

Absorption: Esomeprazole is designed to be taken orally and has an enteric coating to slow down its quick disintegration in the stomach's acidic environment. The variations seen in Cmax, Tmax, and AUC are caused by the differing strengths of oral Esomeprazole (20 mg and 40 mg). When taken without meals, a single oral dosage of 40 mg has a bioavailability of 64% and achieves its peak of 4.7 µmol/L (Cmax) after 1.5 hours (Tmax).

Distribution:

Esomeprazole has an apparent volume of distribution of 16 L. Moreover, esomeprazole has a 97% protein binding rate. This is true for both the intravenous and oral versions.

Metabolism:

The cytochrome P450 enzyme system is responsible for mediating the metabolism of esomeprazole (CYP450). The CYP2C19 isoenzyme forms the hydroxyl and desmethyl metabolites, whereas the CYP3A4 enzyme forms the sulphone metabolite. Every metabolite that forms is inactive.

Excretion:

Esomeprazole's inactive metabolites are mostly eliminated via the kidneys (80%), with a little amount also exiting the body through the feces (20%). Urine contains just 1% of the active parent drug's excretion. Both the oral and intravenous versions of esomeprazole have an elimination half-life of 1-1.5 hrs , with the oral forms having a somewhat longer half-life. There is no drug buildup and total elimination of the substance.

Side Effects:

Headache, diarrhea, nausea, gas, reduced appetite, constipation, dry mouth, and stomach discomfort are typical adverse effects. Severe allergic responses, fever, chest discomfort, dark urine, rapid heartbeat, persistent sore throat, severe stomach pain, unusual bruising or bleeding, unusual weariness, and yellowing of the eyes or skin are more severe side effects.

Proton pump inhibitors may increase the risk of hip fractures and diarrhea linked to Clostridium difficile. The medications are commonly given to patients in critical care as a preventative strategy against ulcers, but their usage is also linked to a 30% rise in pneumonia cases.

Uses

- Used in helicobacter pylori (H. pylori)-associated duodenal ulcer
- Used in NSAID-associated gastric ulcer prophylaxis
- Also helps in gastroesophegeal reflux disease (GERD) with or without erosive esophagitis

Materials and methods

MATERIALS

Aceclofenac and Esomeprazole was obtained from vivimed lab, HPMC was obtained by central lab house, MCC was obtained from JR drugchem PVT LTD, Lactose was obtained from Reckon organics PVT. LTD, SSG was obtained from ,Talc was obtained from , Sodium bicarbonate, Mg stearate, PVP K30, IPA was obtained from Molychem

Method

FORMULATION OF BILAYERED FLOATING TABLETS

Formulation of immediate release layer

The instant release (Aceclofenac) granules were made by sieving all of the excipients (Sodium starch glycolate, Lactose, Talc, Aerosil, and Mg-Stearate) and then combining the drug with other excipients. The granules were employed to create a medication release layer in bilayer floating tablets with an instant release layer.

Tab.2 Composition of various formulations of immediate release layer

Compositions	Formulation code				
	F1	F2	F3	F4	F5
Aceclofenac(mg)	100	100	100	100	100
Sodium starch glycolate. (mg)	5	7.5	10	--	--
MCC	--	--	--	5	7.5
Lactose.(mg)	65	62.5	60	65	62.5
Talc (mg)	5	5	5	5	5
Mg. Stereate(mg)	15	15	15	15	15
PVP K_{30}	q.s	q.s	q.s	q.s	q.s
IPA	q.s	q.s	q.s	q.s	q.s

Preparation of bi-layered floating tablets (wet granulation)

Wet granulation was used to create bilayered tablets with immediate release aceclofenac and sustained release esomeprazole in accordance with the composition. The wet granulation method involves a number of processes, including screening, dry mixing, preparing the binder solution, granulation, and subsequent drying.

Wet granulation Procedure

Granulation of Esomeprazole

Step: 1

Sieving

The active ingredient (Esomeprazole) and the exciepient was passed through sieve #60

Step: 2

Dry mixing

Esomeprazole, Lactose, sodium starch glycolate, MCC were accurately measured and taken in a mortar, then mixed for 5minutes to ensure uniform mixing of the ingredients with the drug.

Step: 3

Preparation of binder solution

In this we are using PVP K_{30} and IPA was used as binder. Mostly 5% binder solution was used (5gm PVP in 100ml of IP)

Step: 4

Granulation

In the mixed ingredients binder solution was added slowly with constant mixing till to get solid mass.

Then this solid mass wass passed through sieve #12 to get uniform granules.

Step: 5

Drying

The wet granules were then allowed to dry in hot air oven at 50^0C for 30-40 minutes because IPA is caustic and evaporates rapidly. Samples were taken out randomly at different time intervals from the total bulk of the granules and checked out for moisture content

Step: 6

Sieving

The dried granules was then passed out from sieve #20 to get uniform seized granules for better flow property.

Tab.3 Composition of various formulations of sustained release layer

Compositions	Formulation code				
	F1	F2	F3	F4	F5
Esomeprazole	40	40	40	40	40
HPMC	85	120	85	110	100
$NaHC0_3$(mg)	70	70	80	70	70
Lactose monohydrate(mg)	90	55	80	65	75
Ferric oxide red (mg)	0.6	0.6	0.6	0.6	0.6
Talc	5	5	5	5	5
Mg stereate	20	20	20	20	20
PVP	q.s	q.s	q.s	q.s	q.s
IPA	q.s	q.s	q.s	q.s	q.s

Lubrication and compression of bilayered tablets

Accuretely weigh Mg stereate and talc and pass through sieve #20. Then mix it with dried esomeprazole in polybag for 5 min. Then the lubricated granules of Esomeprazole and lubricated granules of Aceclofenac drug were added in the separate hopper in double rotary punching machine and compressed into bilayered tablets using 18.6 X 9mm caplet shape punches, at weight of 510 mg each.

POST COMPRESSION EVALUATION OF BILAYERED TABLETS

Physical appearance

Numerous characteristics, including tablet form, smoothness, chipping, fractures, surface texture, color, embossing, and debossing, are measured in order to determine the physical appearance of the compressed tablets. [12]

Weight variation

To guarantee that a tablet contains the right amount of drugs, the weight of the tablet being manufactured is regularly monitored. IP weight variation test was carried out by Weighing each of the twenty tablets separately, calculating their average weight, and comparing it to the average weight . If not more than two tablets fall outside of the % ranges, the tablet passes the IP test. The official IP tablet % deviation limits are shown in (Table 5.7) [13]

Table 4: Limits for weight variation test.

Sl . No.	Average weight of Tablet	Maximum % difference Allowed
1	≤ 80 mg	10
2	80-250 mg	7.5
3	≥ 250 mg	5

Hardness

The hardness of tablets determines their resistance to capping, abrasion, or breaking during handling, transportation, and storage before to use. A hardness tester (Pfizer hardness tester) was used to measure hardness. Six tablets were chosen at random from each batch and assessed. A minimum hardness of approximately 4-6 kg/cm2 is thought to be necessary for mechanical stability for uncoated tablets. [14]

Thickness

Five tablets were taken from each formulation batch, and measured their diameter with a vernier calliper and a screw gauge was used to measure the tablet thicknesses. A calculation was made to determine the average thickness.

Friability

Friability is the generic term for the weight loss of the tablets inside the containers as a result of the particles being removed from the tablet surface. Friability often indicates a lack of cohesiveness among the constituents in tablets. [15]

Method: Ten tablets were weighed first, put in the Roche friabilator, and spin for 100 revolutions at a speed of 25 rpm. After taking the tablets out of the friabilator and cleaning off the dust, they were weighed once more and the final weight was noted.

$$\% \text{ friability} = \frac{\text{initial weight-final weight}}{\text{Final weight}} \times 100$$

Drug content

This test is used to make sure that all of the tablets in a batch have nearly the same quantity of the drug substance that is intended. Due to greater understanding of physiological availability, this test is conducted by consuming twenty tablets randomly, weighed and powdered. In a 100 ml volumetric flask, 0.1 N HCl was used to dissolve an amount of powdered tablet equal to the average weight of the tablet. The sample solution was further diluted, and the following formula was used to determine the percentage of drug content. The absorbance was measured using 0.1N HCl as a blank**.** [16]

$$\text{Concentration} = \text{Absorbance/Slope}$$

$$\text{Drug content (mg)} = \text{concentration} \times \text{dilution factor}$$

$$\% \text{ Drug content} = \frac{\text{Drug content(mg)}}{\text{lable clain(mg)}} \times 100$$

Swelling studies

Tablet swelling occurs when a liquid is absorbed and the weight and volume of the tablet rise. The liquid may be absorbed by the particle because of macromolecule hydration or saturation of the particle's capillary gaps. Particles inflate as a result of the liquid entering them through pores and binding to big molecules, which breaks the hydrogen bond. The tablet provides a way to quantify the degree of swelling in terms of percentage weight gain. A single tablet from each formulation was weighed and put in a petri plate with 10 ml of 0.1N HCl. The tablet was taken out of the petri dish every hour and weighed for a total of five hours. The formula was used to determine the tablet's % weight gain. [15]

Swelling index (S.I) = {(Wt-Wo) / Wo} x 100

Where,

S.I. = swelling index,

Wt = Weight of tablet at time t,

Wo = Weight of tablet before immersion.

Floating Test

The tablets were added to 0.1 N Hcl in a 100 ml beaker. Measurements were made of the amount of time the dosage form remained buoyant after being introduced and the time it took for it to become buoyant on 0.1 N Hcl. The amount of time that the dosage form remains buoyant is known as Total Floating Time (TFT), and the time it takes for it to emerge on the medium's surface is known as Floating Lag Time (FLT) or Buoyancy Lag Time (BLT). [17]

Dissolution studies

The USP dissolution test apparatus Type-II (Paddle type) was used to assess the release of aceclofenac and famotidine bilayer tablet. 900 mL of distilled water were poured to a dissolving vessel, and the medium temperature was kept at 37°C±0.5°C. At 50 rpm, the paddles are rotated. After specific interval, an 5 ml of the sample was taken and replaced with brand-new dissolving media to maintain the sink condition. At 275 and 301 nm, the samples were examined using a UV spectrophotometer.[15]

Micromeritic evaluation

Table 5: Flow properties of aceclofenac IR layer granules

Formulation Code	Angle of repose (θ)	Bulk density gm/cc	Tapped density gm/cc	Carr's index %	Hausner's ratio %
F1	24.78	0.328	0.398	17.5	1.21
F2	25.23	0.317	0.376	15.6	1.18
F3	27.71	0.342	0.410	16.5	1.19
F4	25.76	0.275	0.338	18.6	1.22
F5	28.34	0.426	0.502	15.1	1.17

Table 6 Flow properties of esomeprazole SR layer granules

Formulation Code	Angle of repose (θ)	Bulk density gm/cc	Tapped density gm/cc	Carr's index %	Hausner's ratio %
F1	21.14	0.314	0.381	17.5	1.21
F2	21.22	0.327	0.387	15.5	1.18
F3	24.42	0.284	0.339	16.2	1.19
F4	24.29	0.319	0.391	18.4	1.22
F5	25.68	0.349	0.403	13.3	1.15

Post compression evaluation

Tab 7 Physicochemical evaluations of bi-layered tablets

Formulation	Avg. Weight(Mean ±S.D)	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Drug content (%)
F1	508	5	3.4	1.345	88.5
F2	495	5.2	7.5	0.252	89.1
F3	504	4.9	6.2	0.498	91.4
F4	487	5.4	6.8	0.482	86.3
F5	506	5.2	5.8	0.442	94.4

Floating test

Tab 8: Floating lag time and total floating time

Parameters	Formulation				
	F1	**F2**	**F3**	**F4**	**F5**
Floating Lag Time (sec)	25	61	34	43	30
Total Floating Time (hrs)	>8	>5	>10	>7	>8

Standard calibration curve

Aceclofenac and esomeprazole spectra were generated and scanned using a UV visible spectrophotometer. The solution's absorbance peaks at 275 and 301 nm. The calibration curve for various dosages of esomeprazole/aceclofenac was plotted against absorbance. This was shown in the aforementioned Figures 1 and 2. Aceclofenac's correlation coefficient with ethanol was found to be 0.990.

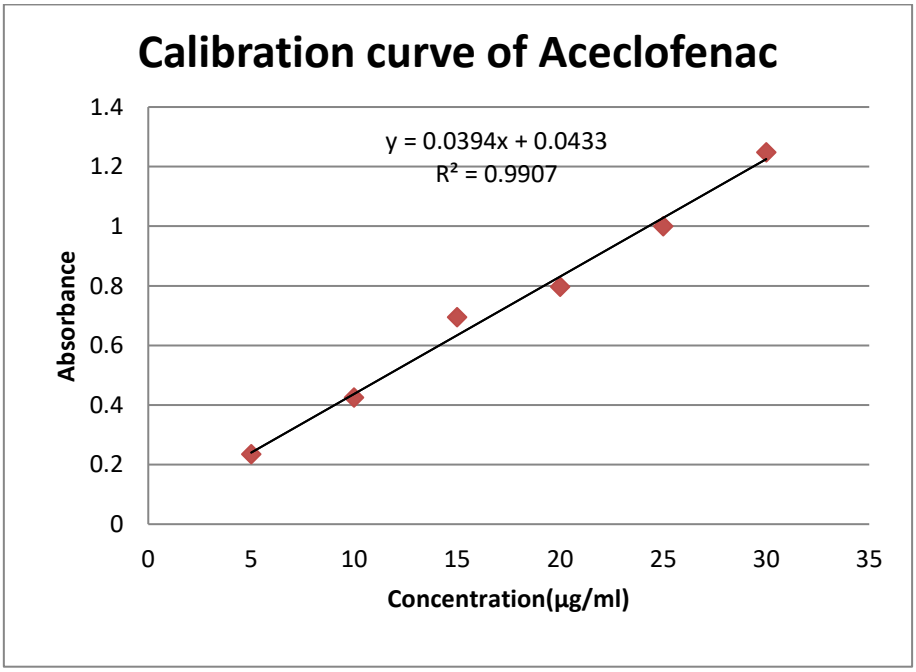

Fig 1 plot of aceclofenac in ethanol Standard

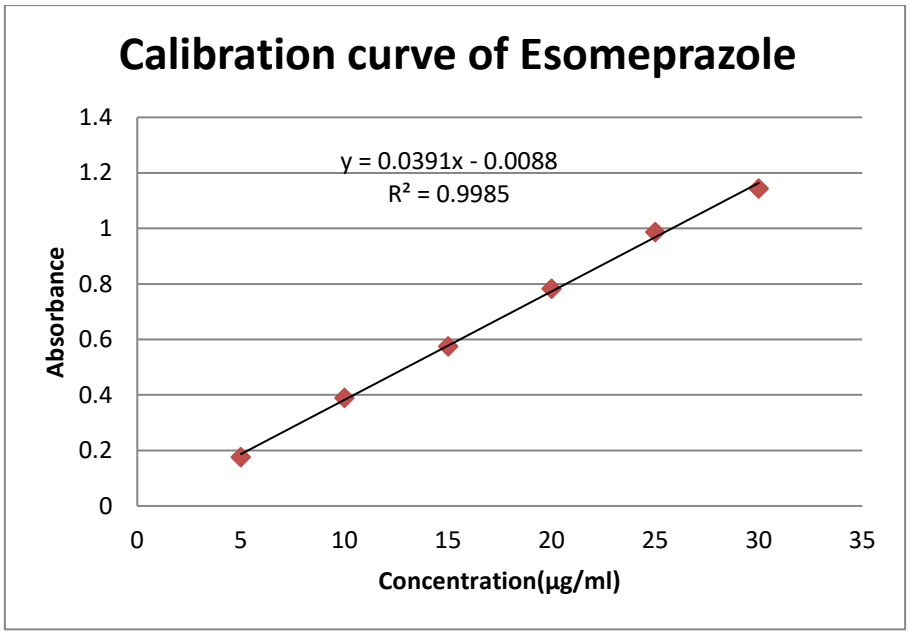

Fig 2 Standard plot of Esomeprazole

DISSOLUTION STUDIES

Table 9 : In-vitro dissolution of Esomeprazole F1-F5

Time (hrs)	F1	F2	F3	F4	F5
1	23.4	9.2	12.5	11.3	17.9
2	42.8	23.2	24.6	23.2	29.8
4	62.6	37.3	35.8	33.1	42.3
6	73.7	48.7	53.6	50.4	56.5
8	89.5	59.5	72.4	63.7	77.3
10	97.4	78.7	87.3	85.6	88.7
12	-	92.3	96.7	93.4	95.6

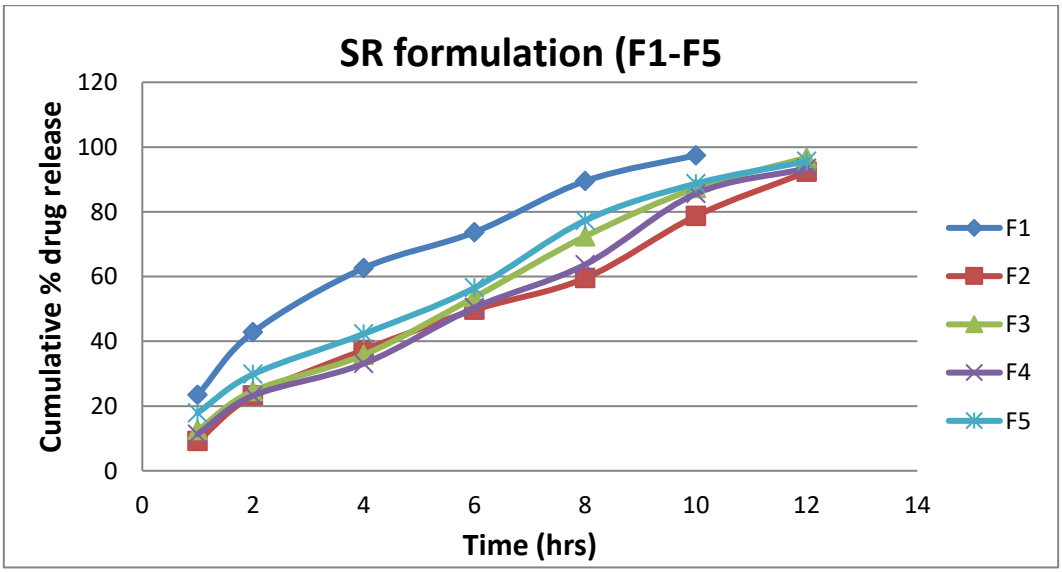

Fig 3 Graph representing Cumulative % Drug Release of drug SR layer of Trials F1-F5 formulations

Table 10: In-vitro dissolution of Aceclofenac F1-F5

Time (min)	F1	F2	F3	F4	F5
5	12.6	18.2	23.2	13.3	20.2
10	25.4	29.2	36.4	23.5	32.6
15	30.8	40.0	44.5	35.1	43.7
20	41.3	49.2	52.5	46.7	53.5
30	53.3	64.5	68.4	59.3	69.6
45	72.6	78.6	84.1	73.4	81.7
60	89.7	91.5	97.4	88.2	93.3

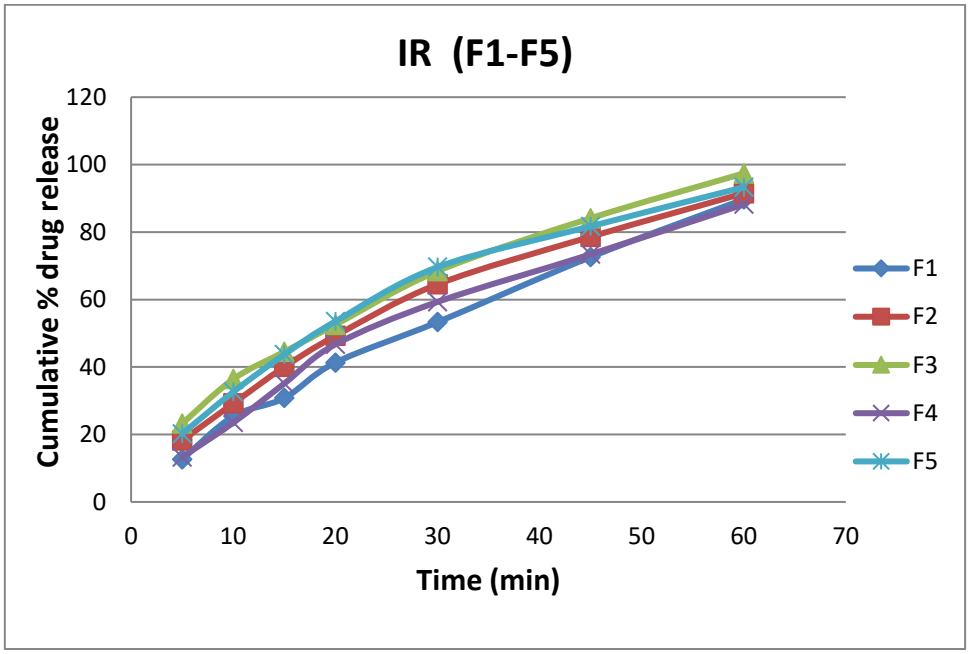

Fig 4 Graph representing Cumulative % Drug Release of drug IR layer of Trials F1-F5 formulation

SUMMARY AND CONCLUSION

- Bilayered floating tablets containing immediate release of aceclofenac using SSG as a super disintegrant polymer and sustained release of esomeprazole using as a retardant polymer and sodium bicarbonate as gas generating agent were successfully produced using the wet granulation process.
- Studies of the FTIR spectra showed that the drug and the polymers were compatible.
- The prepared granules were assessed for precompression studies indicating a good flow characteristic
- The evaluation standards, which included content homogeneity, friability, and hardness, were all within limits for the several batches that were prepared. The optimized formulation has a 94.4% drug content, an average thickness of 5.2, an average hardness of 5.8, an average weight of 506, and a friability of 0.442.

- For batches F1, F2, F3, and F5, buoyancy lag time and total floating time displayed good results. The influence of hardness on floating lag time was assessed for formulation F2, and the findings indicated that floating lag time increased with increasing hardness because of a decrease in porosity.
- In contrast to the other batches, which were unable to maintain their release for more than 10 hours, batch F3 and F5's in vitro dissolution demonstrated a satisfactory drug release rate.
- The best formulation among the five trials was F5, which releases esomeprazole in a similar sustained manner—that is, 12% in the first hour and the remaining drug supply for up to 10 hours—and the same formulation, which releases aceclofenac instantly within an hour.

Overall, tablets of batch F1 and F3 possessed quick buoyancy lag time and good total floating time.

ACKNOWLEDGMENT

I sincerely thank my supervisor Prof**. (Dr.) Ravinesh Mishra**, Dean of Pharmacy, School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences & Technology, and **Dr. Bhartendu Sharma**, HOD of Pharmacy, School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences and Technology, Baddi, Solan, H.P.,for his guidance, help and motivation, and most of all his never-ending support to all my ideas, my success and failures.

References

1. jangid, v., a. chatterjee, and v. agrawal, A Review on Bilayer Tablet Technology for Multi Modal Drug Delivery. Journal of Biomedical and Pharmaceutical Research 2022. **60**: p. 11.
2. thorat, a.n., et al., REVIEW: BILAYER TABLET IS A NEW APPROACH. wORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES, 2023. **12**(5).
3. Kiran, B., et al., BILAYER TABLETS-A REVIEW. International Journal of Pharmaceutical, Chemical & Biological Sciences, 2015. **5**(3).
4. Chawla, G. and A. Bansal, A means to address regional variability in intestinal drug absorption. Pharm tech, 2003. **27**(2): p. 50-68.
5. Garg, R. and G. Gupta, Progress in controlled gastroretentive delivery systems. Tropical journal of pharmaceutical research, 2008. **7**(3): p. 1055-1066.
6. Nayak, A.K., B. Das, and R. Maji, Gastroretentive hydrodynamically balanced systems of ofloxacin: In vitro evaluation. Saudi Pharmaceutical Journal, 2013. **21**(1): p. 113-117.
7. Vinchurkar, K., et al., Features and Facts of a Gastroretentive Drug Delivery System-A Review. Turkish Journal of Pharmaceutical Sciences, 2022. **19**(4): p. 476.
8. Gutierrez-Rocca, J., H. Omidian, and K. Shah, Progresses in gastroretentive drug delivery systems. Business Briefing, Pharmatech, 2003: p. 152-156.
9. Dixit, N., Floating drug delivery system. Journal of current pharmaceutical research, 2011. **7**(1): p. 6-20.
10. Ahmed, I., et al., In vitro release kinetics study of ambroxol hydrochloride pellets developed by extrusion spheronization technique followed by acrylic polymer coating. J. Pharm. Sci, 2008. **7**(1): p. 75-81.
11. Sathiyaraj, M., Bioanalytical Method Development and Validation of Esomeprazole in Human Plasma by Lc-Ms/Ms. 2010, JKK Munirajah Medical Research Foundation, College of Pharmacy, Komarapalayam.

12. Sawanny, R., et al., Gastro Retentive Drug Delivery System: Latest Approach towards Novel Drug Delivery. Research Journal of Pharmacy and Technology, 2023. **16**(1): p. 453-458.
13. Pharmacopoeia, I., Ministry of health and family welfare, Govt. of India. controller of publications, New Delhi, 1996. **736**: p. A80-83.
14. Darkes, M.J. and C.M. Perry, Clarithromycin extended-release tablet: a review of its use in the management of respiratory tract infections. American Journal of Respiratory Medicine, 2003. **2**: p. 175-201.
15. Nijhu, R.S., A. Khatun, and A. Mannan, Formulation and in vitro evaluation of bilayer floating tablet of aceclofenac and esomeprazole by using natural and synthetic polymer. Nat. J. Pharm. Sci, 2022. **2**: p. 33-43.
16. El-Gibaly, I., Development and in vitro evaluation of novel floating chitosan microcapsules for oral use: comparison with non-floating chitosan microspheres. International journal of pharmaceutics, 2002. **249**(1-2): p. 7-21.
17. Dave, B.S., A.F. Amin, and M.M. Patel, Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation. Aaps PharmSciTech, 2004. **5**: p. 77-82.