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Formulation, Development, And Evaluation of Sustained Release Gastro Retentive Floating Tablet of Trifluridine and Tipiracil HCL

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***ABSTRACT**: The present study aims to formulate gastro-retentive floating tablets containing TFD and TP HCl. The floating tablets were prepared using a direct compression method using various polymers like HPMC K4M, HPMC K15M, HPMC K100M, guar gum, and sodium bicarbonate as floating effervescent agents. The formulation was evaluated for hardness, friability, weight variation, swelling index, floating lag time, floating time, and % CDR. 32 factorial designs were optimised by taking the concentration of HPMC K15M and sodium bicarbonate as independent variables and floating lag time and % CDR as dependent factors. The optimised batch of floating tablets (S7) was subjected to the short-term stability study at 40 ±2 0C with an RH of 75% for one month. All the physicochemical properties of the prepared floating tablet were found to be in an acceptable range. The optimum HPMC K15M and sodium bicarbonate concentration were required to formulate floating tablets to increase GRT. From the formulated factorial batches, the S7 batch containing 15% HPMC K15M and 7.5 % sodium bicarbonate xxiii showed the lowest lag time of 25.22 ± 0.41 sec and the highest CDR at 12 hrs. of 98.63% for TFD and 98.48% for TP, respectively. From the results obtained, it was concluded that the optimised formulation containing HPMC K15M and sodium bicarbonate shows better swelling properties with the desired drug release properties and floating behaviour. Hence, HPMC K15M is a potential polymer candidate for formulating sustained-release floating effervescent tablets.*

***KEYWORDS:** Gastric cancer, Trifluridine, Tipiracil HCl, floating tablet, 3^2 factorial designs.*

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I. INTRODUCTION

For many years, oral drug delivery has been recognized as the most popular administration method for systemic drug delivery through a variety of pharmaceutical products with varying dosage forms. One possible explanation for the oral route's widespread acceptance is its simplicity of administration. Limited gastric residence times (GRTs) challenge oral continuous medication administration systems. Since most medications are absorbed in the stomach or upper portion of the small intestine, rapid GI transit can hinder full drug release in the absorption zone and decrease the effectiveness of the dose that is delivered.[2,3] To overcome these limitations, various approaches have been proposed to increase the gastric residence of drug delivery systems in the upper part of the gastrointestinal tract, including floating drug dosage systems (FDDS)[4-5] swelling or expanding systems6, mucoadhesive systems[7,8], modified shape systems[9] high-density system[10], and other delayed gastric emptying devices. Among

FDDS is the most commonly used in these systems. Floating systems, also known as hydrodynamically controlled systems, are low-density systems that provide sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach for an extended period, without affecting the gastric emptying rate. The growth of cells that begins in the stomach is called gastric cancer. Metastatic or localized advanced gastric cancer are both possible. A mutation in the structure of DNA in cells triggers gastric cancer, which can disrupt the cells' growth. Around 782,685 people worldwide die from gastric cancer each year, making it the fourth leading cause of cancer-related death worldwide. Even though both the incidence and mortality rates of gastric cancer have been declining over the last century, it remains the second leading cause of cancer death worldwide. Helicobacter pylori infection has been identified as the most significant risk factor for gastric cancer. It may even be a (nearly) necessary condition for the development of gastric non-cardia adenocarcinoma[11]. Gastric cancer (GC) is a multifactorial disease, with many environmental and genetic factors influencing its development.

According to current statistics, GC is the fourth leading cause of cancer deaths worldwide, with a median survival rate of less than 12 months for the advanced stage. Gastric carcinoma is a highly aggressive malignancy with a heterogeneous nature that continues to be a global health issue. As a result, alternative prevention, such as a proper diet, early diagnosis, and follow-up with proper treatments, leads to a decrease in recorded incidents. GC is relatively uncommon and is not common in the young population (those under 45 years old), with no more than 10% of patients suffering from disease development.[12]

Trifluridine is rapidly metabolized by thymidine phosphorylase (TPase) to inactive forms with decreased cytotoxicity, resulting in its poor bioavailability and toxicity when taken alone. Trifluridine metabolic degradation is systemized by the TPase inhibitor Tipiracil HCl. As a result, the required cytotoxicity of trifluridine is increased when it is combined with tipiracil HCl. To inhibit trifluridine catabolism and increase trifluridine bioavailability, tipiracil is combined with trifluridine in a 1:0.5 ratio. Trifluridine/tipiracil HCl is effectively used in the treatment of cancer.

Floating drug delivery systems are needed to improve absorption and bioavailability. It gives sustained drug delivery. Avoidance of gastric irritation because of the sustained release effect. There is no risk of dose dumping. Gastric retention time is increased because of buoyancy.

II. MATERIALS AND METHOD

Trifluridine and Tipiracil HCl were provided as free samples by Emcure Pharma Ltd. (Ahmedabad), HPMC K4M, HPMC K15M, HPMC K100M, sodium bicarbonate, magnesium stearate, Tabletose, guar gum, and Aerosil 200 were purchased from Colorcon Asia Pvt. Ltd. (Goa). HCl was acquired from S.D. Fine Chemicals (Mumbai, India).

DOSE CALCULATION

Trifluridine		
Dose: 35 mg/m^2(general Human body surface area 1.75 m^2)	61.25	
Volume of distribution (VD) (liter)	25	
Maximum plasma concentration (Cmax) (µg/ml)	2381	583.10
Half-life (hr.)	2.1	

Calculation for loading dose of TFD DL = Cmax × VD = 15 mgMaintenance dose 12 hr. (DT) = DL (1 + 0.693 X T / t1/2) Where DT = Total Dose, DL = Loading dose
Total dose (DT) = Loading dose (DL) + Maintenance dose (Dm)

Total dose of Trifluridine = 15+75= 90mgTipiracil HCl = 90/2 = 45 mg.

Preparation of floating Tablets: -

Trifluridine And Tipiracil HCl in the ratio of 1:0.5 was uniformly mixed. Then all the polymers were added to the mixture of drugs. Diluent, Lubricant and Flow promoter were weighed accurately and the gradual mixing of whole powder was then directly compressed into the tablet punching machine.

Table No.-1: Composition of the formulation in terms of coded and actual value

Run	**Coded Value**		**Actual Value**	
Batch Code	X1	X2	X1 (%)	X2 (%)
S1	-1	-1	2.5	15
S2	-1	0	2.5	20
S3	-1	+1	2.5	25
S4	0	-1	5	15
S5	0	0	5	20
S6	0	+1	5	25
S7	+1	-1	7.5	15
S8	+1	0	7.5	20
S9	+1	+1	7.5	25

Table No.-2: Composition of formulation

Ingredients	S1	S2	S3	S4	S5	S6	S7	S8	S9
Drug (mg)	135	135	135	135	135	135	135	135	135
HPMC K15M (%)	15	20	25	15	20	25	15	20	25
Sodium Bicarbonate (%)	2.5	2.5	2.5	5	5	5	7.5	7.5	7.5
Mg. stearate (%)	1	1	1	1	1	1	1	1	1
Aerosil 200(%)	1	1	1	1	1	1	1	1	1
Lactose (mg)	187	167	147	177	157	137	167	147	127
Total wt. (mg)	400	400	400	400	400	400	400	400	400

Table no. 5.9: Composition of formulation

Evaluation (Pre-compression) of flow properties of powder blends of factorial batches

The characterization of flow properties of powder blends is important in tablet compression. The powder blends with good flow properties gives uniform die fill and consequently it gives the uniform tablet weight.

- **Bulk density**

The bulk density of powder is important parameter in the compressibility of the powder. The bulk density was between 0.34 ± 0.02 to 0.37 ± 0.02 gm/cm^3

- **Tapped density**

The tapped density of powder is important parameters in the compressibility of the powder. The tapped density was found to 0.41 ± 0.01 to 0.45 ± 0.02 gm/cm^3

- **Carr's index**

The Carr's index is indicator of compressibility. The value below 21% shows fair to passable compressibility. It was found to be 11.30 ± 0.02 to 21.53 ±1.31 indicating passable compressibility.

- **Hausner's ratio**

The Hausner's ratio is another parameter indicating the flow properties. The value of ratio below 1.25 indicates good flow while above 1.25 indicates the poor flow. It was found to be 1.1 ± 0.02 to 1.58 ± 0.02 indicating good to passable flow ability.

- **Angle of repose**

The angle of repose can be correlated with type of flow of powder. The angle of repose 31 to 35 indicates the good flow while the angle of repose more 30 indicates poor flow properties and angle of repose below 30 indicates excellent flow properties. The angle of repose was found to be within the range of 27.00±1.12 to 28.00±0.90 indicating good flowability.

Table No. 2: Evaluation (Pre-compression) parameters of all formulations (F1-F12)

Formulation Code	Bulk density (gm/ cm^3) (n=3 ± SD)	Tappeddensity (gm / cm^3) (n=3 ± SD)	Carr's Index (%) (n=3 ± SD)	Hausner'sratio (n=3 ± SD)	Angle of repose (n=3 ± SD)
S1	0.435±0.036	0.519±0.039	16.18±0.017	1.21±0.023	27.12±1.18
S2	0.479±0.012	0.583±0.061	17.83±0.024	1.26±0.042	28.35±1.26
S3	0.486±0.026	0.619±0.081	21.48±0.022	1.30±0.053	29.72±0.78
S4	0.423±0.059	0.540±0.012	21.66±0.039	1.39±0.049	30.67±1.09
S5	0.458±0.027	0.529±0.09	13.42±0.054	1.33±0.031	31.17±0.96
S6	0.472±0.043	0.544±0.032	13.22±0.046	1.28±0.021	28.36±1.21
S7	**0.469±0.052**	**0.537±0.045**	**12.66±0.075**	**1.19±0.061**	**24.99±0.49**
S8	0.408±0.01	0.527±0.029	22.58±0.079	1.22±0.082	26.43±0.28
S9	0.467±0.022	0.572±0.072	18.35±0.082	1.36±0.073	26.76±0.79

POST COMPRESSION STUDIES

1. Weight Variation

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 200 mg tablets and none by more than double that percentage.

2. Hardness test

The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. The hardness of tablet was found in between 3.3±0.30 to 4.3±0.30.

3. Thickness

The Thickness of tablet was measured by Vernier caliper & the Furosemide tablet of thickness were found in between the 2.30±0.45 to 2.70±0.05.

4. Friability test

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the Roche friabilator, rotating at 100 rpm for 4 min. The tablets are then taken out, dedusted and were weighed. The difference in the weight is noted and expressed as percentage.

5. Content uniformity

Twenty tablets were crushed and powder equivalent to weight of one tablet was dissolved in phosphate buffer 6.8. Then suitable dilutions were made and absorbance at 276 nm wavelength was taken by using a UV visible spectrophotometer. The content uniformity of Furosemide were found to be 95.23±1.09 to 99.36±0.48.

6. Disintegration time

Fast Disintegrating tablets apply the tests observe the tablets within the time limit all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely repeat the test on 12 additional tablets, not less than 16 of the total of 18 tablets tested disintegrate completely. The Furosemide tablets were found in between the 14 sec. to 46 sec.

Table No.-3: Evaluation (post-compression) parameters of all formulations:

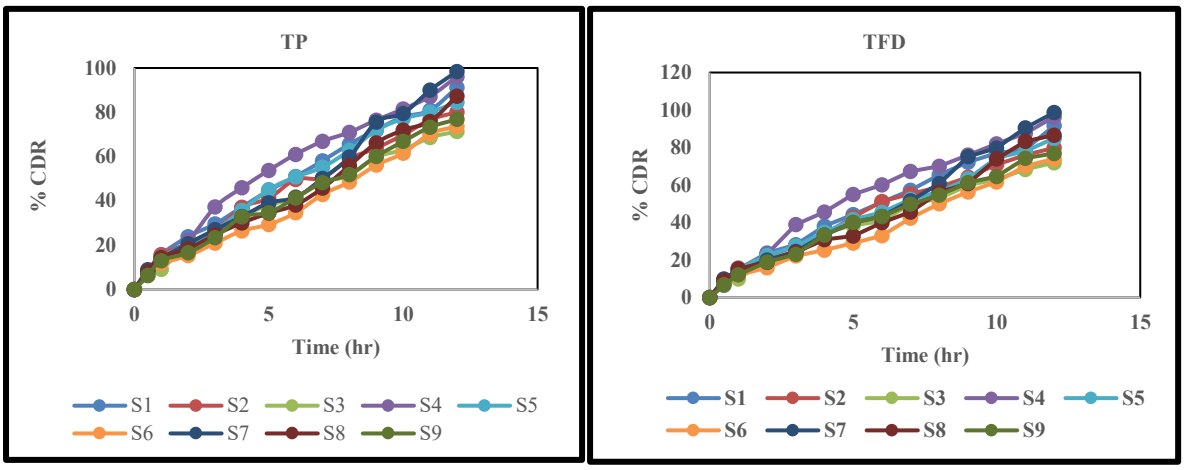
Formulation Code	Wt. Variation n=20(±SD)	% Friability	Hardness n=3 (±SD)	Drug content(%) n=10 (±SD)		Floating lag time (sec) n=3 (±SD)	Total floating time (hr.)
				TP	TFD		
S1	401.30±1.08	0.43	5.45±0.23	97.41	96.76	31.08±0.72	>12
S2	399.03±0.74	0.61	6.11±0.74	98.62	97.09	48.51±0.91	>12
S3	400.24±0.29	0.38	5.61±0.32	97.09	99.61	59.18±1.14	>12
S4	398.48±0.91	0.48	4.83±0.13	97.25	99.27	29.23±1.09	>12
S5	402.05±1.01	0.56	4.53±0.21	99.14	97.56	43.15±0.79	>12
S6	401.19±1.42	0.48	4.89±0.84	99.47	97.39	52.30±0.91	>12
S7	400.58±0.79	0.37	5.36±0.11	99.85	99.61	25.22±0.41	>12
S8	398.85±1.26	0.42	5.14±0.56	98.65	98.18	38.13±1.06	>12
S9	399.69±1.32	0.53	5.50±0.31	98.27	99.33	42.15±0.80	>12

All values are represented as mean ±standard deviation (n=3)

Thickness, hardness, weight variation, & drug content are mean of n determination values are given in mean ± standard deviation.

In-vitro drug release studies:

The in – vitro drug release data of the factorial batches showed the release in the range of [71.35 for TP & 71.96 for TFD] to [98.48 for TP & 98.63 for TDF]. The maximum drug release was found to be 98.48 for TP & 98.63 for TFD in S7 Batch



FTIR RESULT

FTIR studies were conducted and the spectrum was recorded in the range of 4000-400cm-1.No significant interaction between drug and Excipients was observed. All the spectrum i.e. drug and Excipients were concordant with that of standard IR spectra of pure drug .

Figure No 1: FTIR spectra of Trifluridine

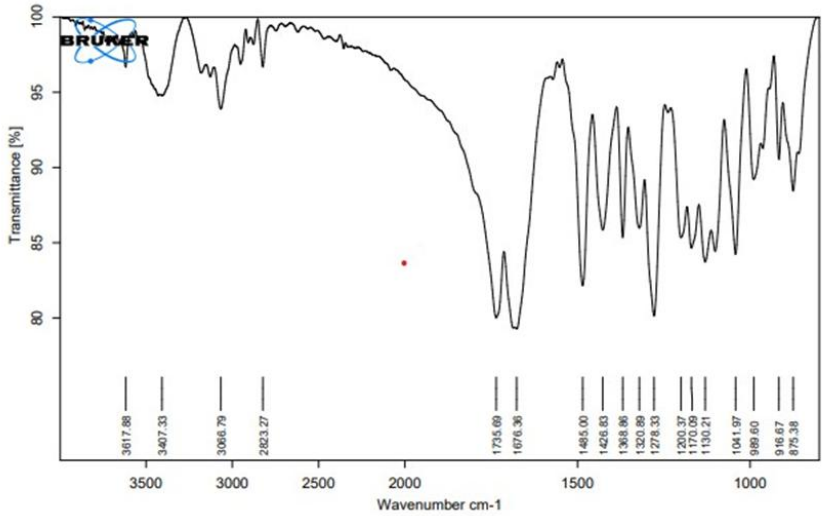
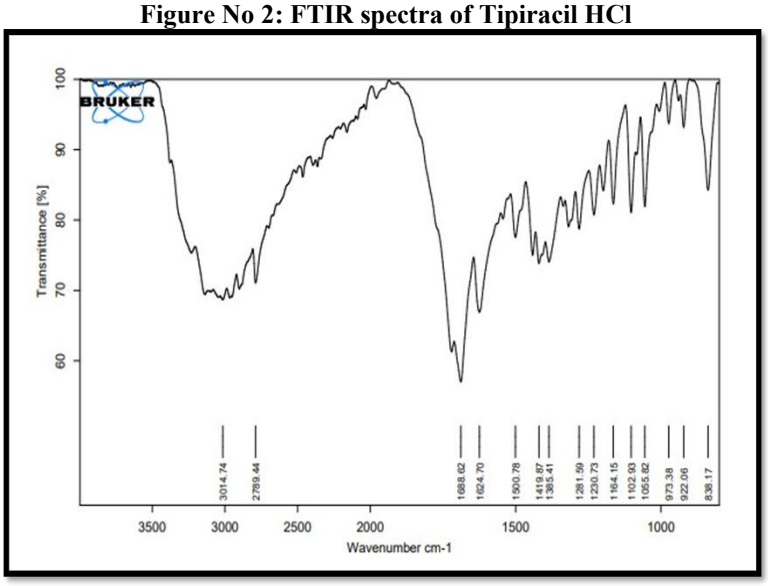


Figure No 2: FTIR spectra of Tipiracil HCl



Functional goup	TFD	TFD + HPMC K4M	TFD + HPMC K15M	TFD + HPMC K100M	TFD + GUAR GUM
-OH	3407.33	3416.69	3419.79	3413.74	3412.12
-NH	3066.79	3182.77	3067.26	3067.30	3068.09
-CH	2823.27	3825.33	2953.89	2824.94	2824.34
C=O	1676.36	1677.73	1678.35	1677.80	1677.44
C-F	1278.33	1278.40	1278.40	1278.12	1278.22

Table No.4- List of Functional Group

ANOVA for floating lag time (Response 1)

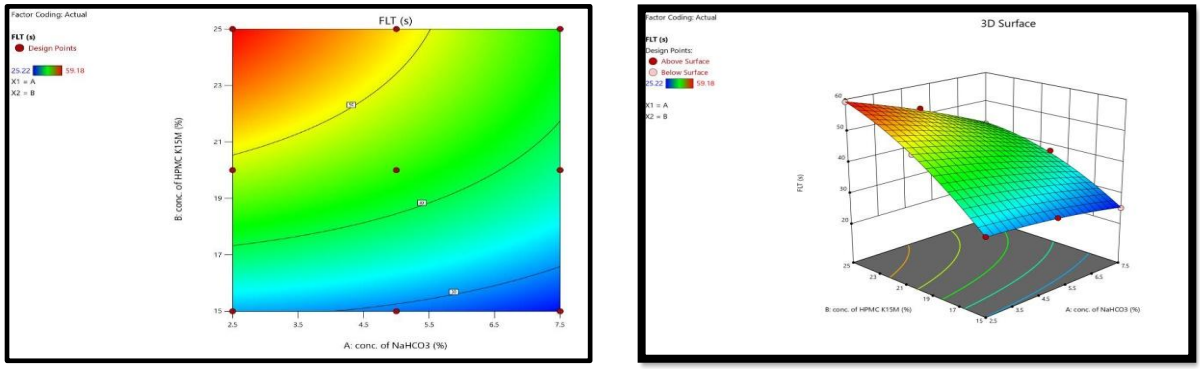
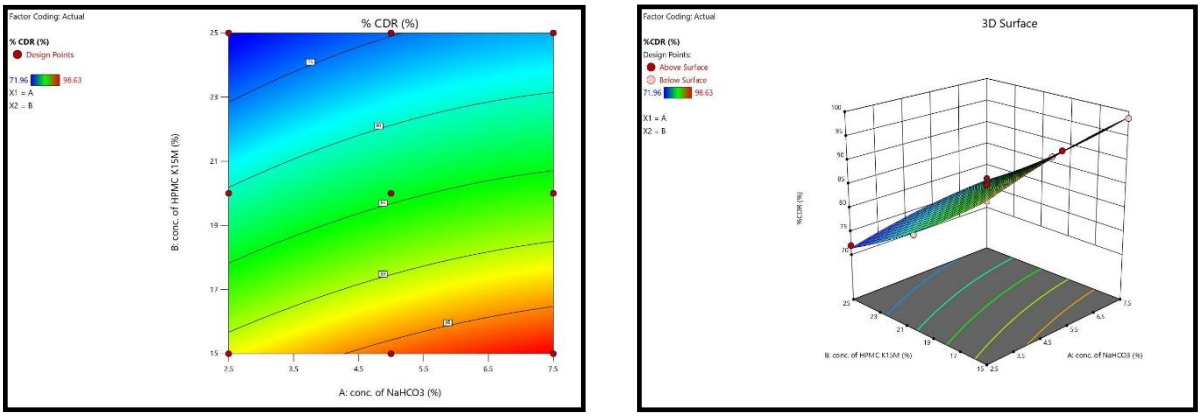


Figure no.: Contour plot and surface response plot showing the effect of Sodium bicarbonate (X1) and HPMC K15M (X2) on response Y1 (Floating lag time)

ANOVA for % CDR (Response 2)



Overlay plot

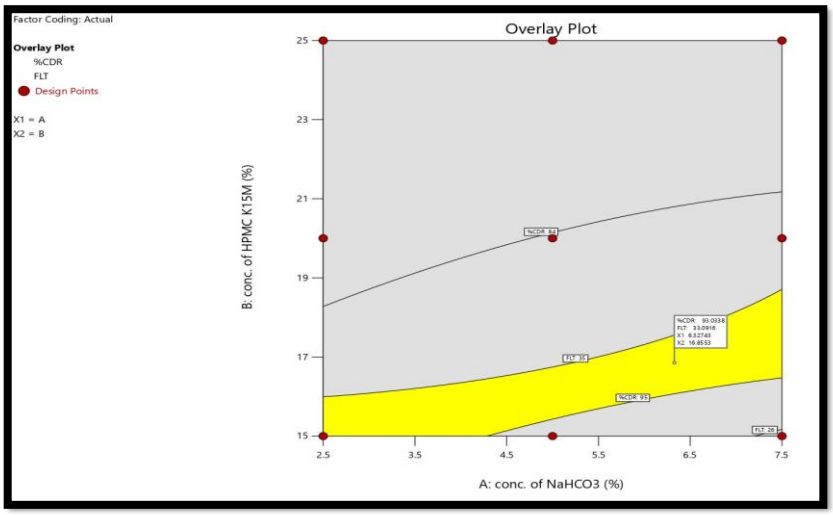
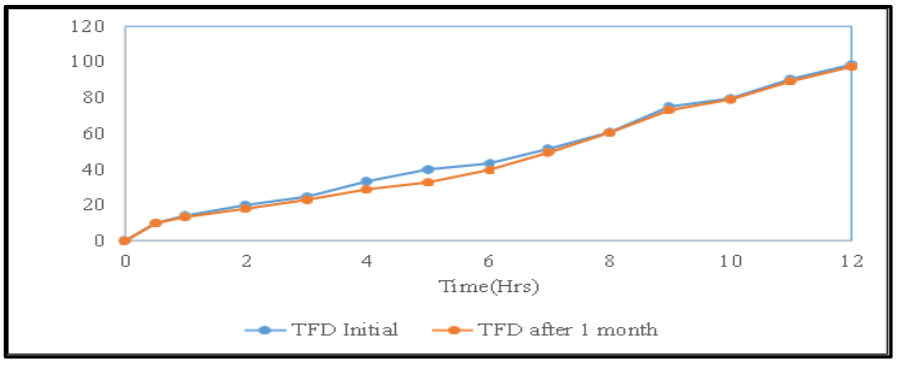


Table No.9: Kinetic release fit model of optimized Formulation

Optimized formulation	Zero-order (R^2)	Firstorder (R^2)	KorseyPeppas (R^2)	Higuchi (R^2)	Hixon Crowell (R^2)
S7	0.989	0.9659	0.9683	0.9214	0.9859

STABILITY STUDIES

Parameters	Initial		After 1 month	
Floating lag time (sec)	25.22 ± 0.41		25.21 ± 0.39	
Floating time (hrs.)	>12		>12	
% CDR at 12 hr.	TFD	TP	TFD	TP
	98.63	98.48	97.11	97.51
Drug content	TFD	TP	TFD	TP
	99.61	99.85	98.89	98.57



III. CONCLUSION

The research aimed to formulate, develop and evaluate the floating tablets of a combination of TFD & TP for effective treatment of gastric cancer. The tablets were prepared by taking various concentrations of polymers as a release retarding agent and sodium bicarbonate as an effervescent agent. The polymers used were HPMC K4M, HPMC K15, HPMC K100M and Guar gum. Before formulation, pre-formulation studies were conducted using FTIR spectroscopy to establish compatibility between the drug and polymers. The results revealed that the drug and polymers were satisfactorily compatible, without any significant changes in the chemical nature of the drug. The powders were evaluated for angle of repose, bulk density, tapped density, Carr's index & Hausner's ratio. The tablets were evaluated for hardness, friability, weight variation test, drug content, in vitro release & floating lag time. Among all the formulations F4 was found best in polymer and its concentration.

The pre-compression and post-compression parameters are within limits. Based on data of in-vitro drug release pattern of preliminary batches it was observed that the most significant sustained release action was observed in batch F4 containing HPMC K15M giving 84.84% & 83.61% release for TFD & TP respectively. Further, the tablets were optimized using 3^2 factorial design to study the effect of HPMC K15M & sodium bicarbonate on response parameters. From the formulated factorial batches, the S7 batch containing 15% HPMC K15M and 7.5% sodium bicarbonate showed the lowest lag time of 25.22±0.41 sec and the highest % CDR at 12 hr. of 98.63 % & 98.48% release for TFD & TP respectively. A stability study was carried out at 40 ± 2°C with 75% RH for a period of 1 month to know the influence of temperature and relative humidity on floating lag time, floating time, drug content and drug release. From the stability studies, it was observed that there were no significant changes in the drug content and In vitro release study of optimized S7 formulation, and therefore the formulation is stable.

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