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Formulation and *In-vitro* evaluation of capecitabine floating tablet

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Abstract
The present research investigation carried out was aimed to develop a Floating tablet of Anticancer Drug Capecitabine. Floating Tablet was formulated using HPMC K15M, Carbomer 934, Sodium Alginate, Sodium Bicarbonate, and Citric Acid which is prepared by wet granulation technique. The prepared Tablet was evaluated for physical parameter, Swelling index, buoyancy Lag Time and in vitro drug release. Based on the % drug release, swelling index, floating lag time and floating time, formulation C2 was an optimized formulation. Formulation C2 showed 91.77% drug release at the end of 24 h. Floating lag time was found to be 38 sec. These tablets showed matrix integrity for more than 24h. Formulations which have higher swelling index shows sustained release of drug in formulation. FTIR Studies shows there was no interaction found between any excipient and drug.

Keywords: Floating tablet, Capecitabine, floating time, swelling index.

Introduction
Gastric floating drug delivery (GFDD) offers a number of benefits for drugs with poor bioavailability because of narrow absorption window in the upper part of the gastrointestinal tract. The gastric emptying time mainly depends upon on the design of the dosage form and physiological state of the subject, which last from a few minutes to 12hrs. [1, 2] The average gastric emptying time in human is 2-3hrs through major absorption zone (stomach and upper part of the intestine), which leads to incomplete drug release from the DDS leading to diminished efficacy of the administered dose. [3, 4] So drugs which have stability problem, GRDF plays an important role. These considerations have led to the development of oral controlled release dosage forms possessing gastric retention capabilities.
GRDF will also greatly improve the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at the gastric mucosa, which are sustained over a long period of time [5-6].
Capecitabine is a prodrug that is selectively tumour-activated to its cytotoxic moiety, fluorouracil, by thymidine phosphorylase, an enzyme found in higher concentrations in many tumors compared to normal tissues or plasma. Fluorouracil is further metabolized to two active metabolites, 5-fluoro-2'-deoxyuridine 5'-monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP), within normal and tumour cells. These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N5-10-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deaxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, therefore a deficiency of this compound can inhibit cell division. Secondly, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis through the production of fraudulent RNA [7-8].

Material and Methods
Materials
Capecitabine was obtained as gift sample from S Khandelwal laboratories Pvt. Ltd. Mumbai. The Carbopol 934 & HPMC K4M was obtained as gift sample from Torrent Laboratory Ltd., Ahmadabad, India. All other materials used of analytical grades.

Preparation of Floating Tablets

The floating tablets of Capecitabine were prepared by wet granulation method. Capecitabine was mixed with carbopol 934, HPMC K4M, sodium alginate, sodium bicarbonate, citric acid & lactose. All components were mixed for 10 min & isopropyl alcohol was added dropwise to make a good wet mass of granules. After remixing for 5 min the granule were passé through a 40 no. mesh sieve. Wet granules were put in a 40^0c oven for 40 min to become dry, and talc and magnesium stearate were added to the granules as lubricating agents. Eventually, 310mg of mixture was and fed into the die of single punch machinery and compressed using 10 mm concave punches.

Table 1: Formulations of Floating Tablets of Capecitabine.

Ingredients in mg	C1	C2	C3	C4	C5	C6	C7	C8
Capecitabine	150	150	150	150	150	150	150	150
Carbopol 934	15	15	10	10	15	15	10	10
HPMC K4M	50	50	50	50	30	30	30	30
Sodium alginate	20	30	20	30	20	30	20	30
Sodium bicarbonate	35	35	35	35	35	35	35	35
Citric Acid	10	10	10	10	10	10	10	10
Talc	4	4	4	4	4	4	4	4
Magnesium. Stearate	9	9	9	9	9	9	9	9
Lactose	16	6	32	12	37	27	42	38
Total weight (mg)	310	310	310	310	310	310	310	310

Evaluation of tablets

Tablet thickness

The crown thickness of individual tablets is measured with a Vernier Caliper. The crown thickness of individual tablets is also determined for the purpose of determining the density of tablet compacts [9].

Hardness

Hardness of the tablet is determined using Monsanto hardness tester. The tablet to be tested is placed between the spindle and anvil and pressure is applied by turning the knurled knob just sufficiently to hold the tablet in position. The reading of pointer on scale is then adjusted to zero. The pressure is now increased as uniformly as possible until tablet breaks. The pointer now reads the pressure required to break the tablet.

Weight Variation Test

Twenty tablets were accurately weighed and an average weight was calculated. Not more than two of the individual weights deviate from the average weight by the percentage deviation given in the table 2

Table 2: I.P. Standards for Uniformity of weight.

Sr. No	Avg. wt. of tablet	% of deviation
1	80 mg or <	±10
2	> 80 to < 250 mg	±7.5
3	> 250 or more	±5

Friability

Twenty tablets were accurately weighed and placed inside the chamber of friabilator. The apparatus was rotated for 100 revolutions. After rotations, the tablets were weighed and the loss in weight was determined. The loss in weight should not be more than 1%.

% Friability = Initial wt- final wt/ Initial wt ×100

Drug Content

Drug content from the tablets was determined by taking tablets from each formulation. Twenty tablets from each formulation were accurately weighed and powdered. Powder equivalent to 150mg of the drug was weighed and transferred into a volumetric flask using 100 ml of 0.1N HCL. A suitable volume of filtrate was diluted with a sufficient quantity of 0.1N HCL to produce a solution containing 10mcg of Capecitabine. The absorbance was measured at 303 nm [10].

Floating lag time

The time between the introduction of tablet and its buoyancy on the 0.1N HCl was measured.

Buoyancy Time

The time during which dosage forms remain buoyant was measured

Swelling Index [11-12]

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium 0.1N HCl at 37±0.5 ^{0}C. After 2,4,6,8,10,12,14,16,18,20,22, and 24 h, each dissolution basket containing tablet was withdrawn, blotted with tissue paper to remove the excess water and weighed on the analytical balance (Schimadzu). The experiment was performed in triplicate for each time point and fresh samples were used for each individual time point. Swelling index was calculated by using the following formula [13].

$$\text{Swelling index} = \frac{(\text{Final weight of tablet} - \text{Initial weight of tablet})}{\text{Initial weight of tablet.}} \times 100$$

In vitro Drug Release

In vitro dissolution tests were conducted in triplicate for all formulations in a USPXXII tablet dissolution apparatus (Electrolab, TDT- 08L) for 12 h under sink conditions. The dissolution medium was 900 ml 0.1N HCl at 37±0.5 ^{0}C. The speed of rotation was maintained to 50 r.p.m. At a predetermined time intervals, 5 ml sample was withdrawn and diluted and absorbance was recorded. The samples were analyzed for drug release by measuring the absorbance at 303 nm using spectrophotometric method (Schimadzu UV) [14].

Infrared spectroscopy

The FTIR of pure drug and physical mixture of formulation ingredients of optimized batch was measured using Fourier transform infrared spectrophotometer (Model FTIR- 8400S,

Shimadzu, Japan). The amount of each formulation ingredient in the physical mixture was same as that in the optimized batch. The pure drug and physical mixture were then separately mixed with IR grade KBr. This mixture was then scanned over a wave number range of 4000 to 400cm-1 [15-17].

Stability Studies

Stability testing of formulation batch was carried out to determine the stability of drug and carrier and also to determine the physical stability of formulation under accelerated storage condition at 45ºC/70%RH. The prepared tablets were placed in borosilicate screw capped glass containers. The samples were kept at condition of 45 °C/70% RH and were analyzed at 7th, 14th, 21st and 28th days for drug content, hardness and *in-vitro* dissolution study [18].

Result and Discussion

The bulk density was found in the range 0.28-0.305 gm/ml. The tapped density was found in the range 0.310-0.341 gm/ml. compressibility index was calculated. It was found in the range 6.45-15.15 %**.** Angle of repose was found in the range 14.03^0-$21.80^{0.}$ The good Flow ability of granules was evidenced with angle of repose and this was further supported by lower compressibility index values.

Table 3: Evaluation of powder blend

Batch	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio	Angle of Repose
C1	0.32±0.1	0.33±0.38	9.09±0.22	1.11±0.33	17°48±0.39
C2	0.30±0.4	0.34±0.27	11.76±0.32	1.13±0.61	16°69±0.12
C3	0.29±0.2	0.32±0.16	9.37±0.15	1.1±0.58	19°79±0.27
C4	0.29±0.3	0.33±0.42	12.12±0.41	1.17±0.39	18°77±0.50
C5	0.28±0.5	0.33±0.18	15.15±0.35	1.17±0.13	15°1±0.44
C6	0.29±0.1	0.31±0.33	6.45±0.39	1.06±0.18	17°48±0.58
C7	0.29±0.4	0.32±0.55	9.37±0.51	1.1±0.26	20°3±0.31
C8	0.29±0.6	0.33±0.22	12.12±0.52	1.13±0.24	21°3±0.62

Evaluation of Capecitabine floating Tablets

Tablets were obtained in the range with acceptable weight variations as per Pharmacopoeia specifications, less than 5%. The thickness of the tablets was found in the range 3.064 mm – 3.116 mm. Uniform thicknesses were obtained due to uniform die fill. Hardness of the tablets was found in the range 5.58-5.91 kg/cm^2. Friability of tablets was observed in acceptable range 0.13-0.47 (Less than 1%). The drug content of the tablets was found between 96.00 to 104.00% of Capecitabine floating tablet.

Table 4: Physical parameters of Tablets.

Batch	Average Weight (mg)	Thickness	Hardness	Friability %	Drug Content (%)	Avg. Lag Time (Sec.)	Buoyancy Time (Hrs.)
C1	312±0.19	3.084	5.75±0.2	0.33±0.51	96.00±02	49	24
C2	306±0.28	3.108	5.75±0.4	0.13±0.28	98.90±04	38	24
C3	303±0.31	3.09	5.75±0.2	0.13±0.06	99.40±01	51	24
C4	313±0.37	3.09	5.66±0.2	0.20±0.24	98.55±03	55	24
C5	315±0.47	3.10	5.58±0.2	0.33±0.16	99.10±02	39	23
C6	308±0.29	3.11	5.66±0.2	0.46±0.18	97.40±05	47	23.5
C7	311±0.15	3.06	5.83±0.2	0.33±0.62	96.25±06	43	24
C8	307±0.41	3.064	5.91±0.2	0.47±0.12	97.70±0.3	58	22

***In Vitro* Dissolution Studies**

From the results it can be observed that though the polymers HPMC K4M, Sodium Alginate has sustaining effect on a release of drug from floating tablet, but increasing concentration of polymer on the formulation retards the release of capecitabine from the tablet. From the formulation C1 to C4 shows retarded release of drug because of higher conc. of polymer, amongst these formulation C2 shows drug release i.e 91.77% at 24 hrs. due to high conc of HPMC K4M &Sodium Alginate would promote the formation of highly viscous gels upon contact with aqueous fluid. This would promote retardation of drug release rate. Formulations C5 to C8 shows95.48%, 96.23%, 95.69% and 98.10% respectively wich have more drug release than C1 to C4.

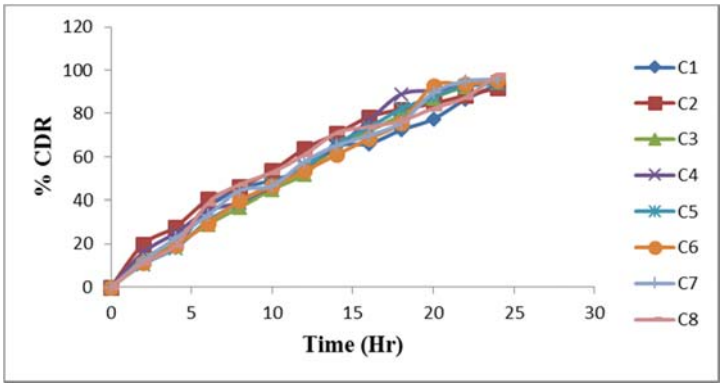

Fig 1: Cumulative drug release of floating tablet of Capecitabine

Swelling Index

Swelling increases as the time passes because the polymer gradually absorbs water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is continuous towards new exposed surfaces, thus maintaining the integrity of the dosage form. The swelling rate of tablets increased in the case of formulation C2 containing Carbopol 934 and HPMC K_4M. The swelling index was increases with the increasing concentration of HPMC K4M due to quick hydration due to high cross linking of polymer which increases the water absorption in floating tablet.

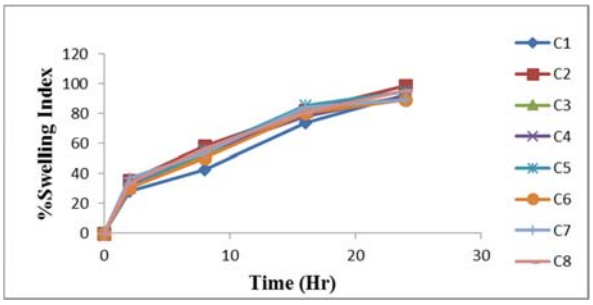

Fig 2: Swelling Index of Capecitabine

Infrared spectroscopy

It was carried out to check for the possible Drug-Excipients interaction. The IR absorption band in cm^{-1} of the drug and excipients used in the study were similar. The IR spectrum did not show presence of any additional peaks for new functional groups indicating no chemical interaction between Drug & the used polymers. From the IR spectrum of the Drug and polymer it was found that there is no or negligible change is observed in the spectrum (which shown in figures) so, there was no chemical interaction observed between drug and excipients (polymers). In this way compatibility was studied between drug and excipient and they are stable.

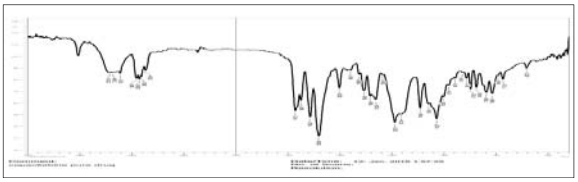

Fig 3: FTIR Spectra of Capecitabine

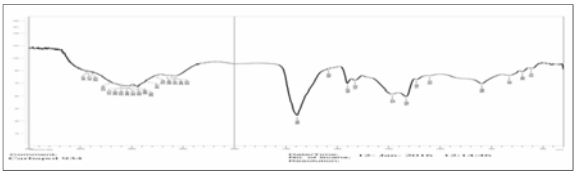

Fig 4: FTIR Spectra of Carbapol 934

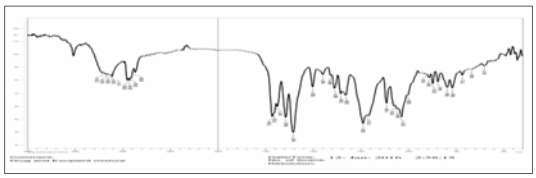

Fig 5: FTIR Spectra of Physical mixture

FTIR spectra of optimized formulation of drug with polymers Carbopol 934 and HPMC K_4 M, showed characteristic peaks of drug at 3437.15, 3386.86 cm^{-1} band for aromatic stretching of O-H group,2916.37 cm^{-1} for C-H stretching in methylene group, 1571.99 and 1458.18 cm^{-1} for aromatic C=C stretching, 1375.25cm^{-1} for methyl group of C-H stretching, 1159.88cm^{-1} for C-F stretching, 1055.85cm^{-1} for sulphoxide group of S=O stretching; and Carbopol 934 peaks appeared at 1518.15cm^{-1} for C=O stretching; and HPMC K_4 M peaks were appeared at 1319.31 cm^{-1} and 1188.15cm^{-1} for C=O stretching; and the peaks at 3412.05cm^{-1} is responsible for hydroxyl group O-H stretch of both polymers Carbopol 934 and HPMC K_4 M. These results were indicates there was no drug polymer interaction after processing of the drug into formulation.

Stability Study

Accelerated stability studies (AST) was carried for optimized formulation C2 by exposing it to 40 °C/75% RH for one month and analyzed the sample at the interval of 7,14,21,28 days. The sample was analyzed for drug content, hardness and cumulative percentage drug release

Table 5: AST of F3 formulation

Parameters	Days		
	15	30	45
Hardness	5.75±0.13	5.67±0.1	5.80±0.13
Drug content (%)	98.46±0.81	98.71±0.32	98.52±0.68
In-vitro dissolution study	91.18±0.21	91.52±0.58	91.26±0.42

Conclusion

The floating tablets were prepared successfully. Floating Tablet was formulated using HPMC K15M, Carbomer 934, Sodium Alginate, Sodium Bicarbonate, and Citric Acid which is prepared by wet granulation technique. The prepared Tablet was evaluated for physical parameter, Swelling index, buoyancy Lag Time and in vitro drug release. Based on the % drug release, swelling index, floating lag time and floating time, formulation C2 was an optimized formulation. Formulation C2 showed 91.77% drug release at the end of 24 h. Floating lag time was found to be 38 sec. These tablets showed matrix integrity for more than 24h. Formulations which have higher swelling index shows sustained release of drug in formulation. So that sustained release floating tablet of Capecitabine can be prepared by using above mentioned polymers in specified concentration.

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