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FORMULATION AND OPTIMIZATION FLOATING TABLETS OF APRICITABINE BY USING COMBINATION OF POLYMERS SUCH AS GANTREZ MS AND HPMC

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ABSTRACT

The principle of the present work was to develop, optimize gastric floating drug delivery system (GFDDS), in vitro, and in vivo evaluation of containing Apricitabine as a model drug and using polymer blend derived from Gantrez ms and HPMC. The effects of independent variables on dependent variables, i.e. floating time, total floating time (TFT), and diffusion exponent (n) and mean residence time (MRT) in the stomach were evaluated. Twenty formulations were prepared, by changing the concentration of Gantrez AN-119, Gantrez MS-995, Gantrez S-97 and HPMC K100M, HPMC K15M from this optimized formulation was found by in vitro dissolution studies obtained was applied to the Zero order, First order, Higuchi and Krosmeyer–Peppas equations. The *invivo* studies of optimize formulation and 2% of suspension was evaluated as float duration up to 24hrs and sustained drug release was obtained. It can be concluded that floating matrix tablet of Apricitabine prepared by using Gantrez ms and HPMCK100M has possible for sustained release of the drug as well as enhanced oral bioavailability through better gastric residence time of formulation in stomach of rabbits.

INTRODUCTION

Floating tablets are used to prolong drug delivery with help of gastric residence time. The tablet will be buoyancy in the stomach without disturbing the gastric emptying rate.[1] The most preferable drugs used in floating drug delivery system which having the locally action of gastrointestinal tract, drug which less absorbed in the intestine and high absorb in stomach. Drugs which have a poor bioavailability have an absorbed in the upper part of gastrointestinal tract (GIT). Floating tablets maintain at the place of absorption, and the longer retention enhances the bioavailability.[2]

Floating tablet can be prepared by several methods which have been developed gastric residence time in stomach and maintained extended releases. The most approaches of theses system are bioadhesive system, swelling and expanding systems, and delayed gastric emptying devices.[3] Floating tablets have a bulk density less than the of gastric fluids and so it remain buoyant on the stomach and produced prolong the gastric retention time.[4]

Apricitabine it was used for a nucleoside reverse transcriptase inhibitor (NRTI) which is interferes with the process of HIV replication by imitating the nucleosides and produce new HIV genetic material.[5] The main mechanism of action of drug is interfered with the DNA strand, thus inhibiting HIV reproduction. The half of drug is 6hrs and bioavailability is less by using floating tablet absorbance was increases.[6]

MATERIAL AND METHODS

Apricitabine gift sample from AVANSCURE LIFESCIENCES PVT LTD, Gurgaon, Haryana, India. Gantrez AN-119, Gantrez MS-995, Gantrez S-97, HPMC K100M and HPMC K15M gift sample from Dr. Reddy lab Hyderabd ., Pharmacel 101, PVPK30, Purified water, Lactose Monohydrate, Citric acid, Sodium bi carbonate, Magnesium Stearate purchase form S.D Fine Chemicals, Mumbai.

Granulation

The granulation was done by wet granulation technology first intra-granulation was done with drug and Pharmacel 101 was triturated with motor and pestel. The mixed powder was granulated by using water contained pvpk-30 solution the wet mass passes through sieve no 44. The extra-granulation was done by mixing the powder of each formulation as given in table 1. The extra-granulation powder mix with intra-granulation in polyethylene bag for 10 min the obtained granules were compressed using 8mm round flat punch on 8 station chemak rotary tablet machine.[7,8]

Pre-compression evaluation

Granule size analysis

The granules size distribution was evaluated by using sieves analysis method, in this method vibration of sieve shaker (Retsch GmbH, Haan, Germany) is done for 5min as a set of standard sieves arrange in the range of 50–2000 nm in a sieve shaker.

The granules were evaluated for flow property i.e. angle of repose, bulk density, tapped density, compressibility index (Carr's index) and Hausner's ratio[9,10] using standard procedures as show in table 2

Post-compression evaluation

The tablet hardness was evaluated by using Monosanto hardness tester for all formulation by the crushing the tablet diametrically. The friability of the prepared tablets of each formulation (n = 10) was tested by using Roche friabilator, at a speed of 25 rpm for 4 minutes up to 100 rotations. The tablets weight was measured by using electronic balance selecting ten tablets of each formulation were selected randomly.[11]

Determination of Floating Lag Time and Total Floating Time: The floating lag time (FLT) is the time requires to rise up tablet from the bottom to the surface of solution contain 0.1N HCl in a 100ml beaker and total floating time (TFT) is measured time to taken float the tablet on the 900ml of 0.1N HCl solution. To determine the FLT, tablets (n = 4) were put on 900ml of 0.1N HCL in a beaker, and the time is required for a tablet to rise on bottom to surface of liquid was measured. Then, the TFT of each formulation was measured which was on the surface liquid of the tablet.[12]

Swelling studies: The swelling property of tablets was study of each formulation by placing the tablet in USP dissolution apparatus II. The dissolution medium was utilized for this study i.e., 0.1N Hcl, 900ml of was taken and rotation speed was 50 maintained. At specific time interval tablet was taken out form the dissolution medium and wipe the tablet with tissue paper weight the tablet. The increasing the tablet weight was measured at every time interval by using the following equation. In this equation w_1 is the initial tablet weight, w_2 is the after swelling tablet weight and SI indicate swelling index.[13,14]

$SI=w_2-w_1/w_1$

***In vitro* Release Study:** The *in vitro* dissolution test was performed by using electro lab eight station offline dissolution apparatus for 24 hours in dissolution medium which contain 900ml of 0.1N HCl. The dissolution apparatus was rotate by using paddle at 50rpm speed at a temperature of 37° ± 2°C. The suitable interval of time the sample was withdrawn of 10ml from dissolution media and measured the absorbance of drug by using UV spectrophotometer at 214nm which was double beem spectrometer analytical mode and 10ml of 0.1N HCL was replaced o dissolution medium to make volume stable.

Kinetic Modeling of Release Profiles: The mechanism of drug release was estimated by the zero-order, first order, Higuchi equation and korsmeyer-peppas, and Hixson-crowell by taking the dissolution studies.[15,16] The estimation of which type of drug release was obtained and swelling studies was estimated to support mechanism of drug release. The mechanism drug release from the formulated tablets was estimated by zero order by drawing graph between time vs cum % drug release. The drug release data was fitted to the exponential equation i.e., Kormeyer equation. In this equation they are represent M_t and M_f as amount of drug release at time and infinity. K is represent as rate constant and n values it is used for diffusion exponent which indicates the mechanism of drug release.[17,18] The graph was drawn between log times verse log % cumulative drug releases from that n values obtained which in the range was $0.45<n<0.89$ indicate that fickian release (case I) above the value 0.89 indicate non fickian release (anomalous) super case II transport and mechanism of release was to a combination of both diffusion and erosion controlled drug release.[19,20]

$M_t/M_F= K\ t^n$

***In vivo* evaluation**

The pharmacokinetic evaluation parameters such as maximum plasma concentration was estimated by C_{max} (ng/mL), maximum time of plasma concentration is estimated by T_{max} (h) and it is obtained by plasma concentration with time profile with area under curve, the elimination rate constant was estimated by Kel (h^{-1})was calculated by log linear regression , the elimination half-life of drug $t_{½}$ (h), area under curve within 24 hours AUC_{0-24} (ng.h/mL) was calculated by trapezoidal rule, area under curve at infinity $AUC_{0-\infty}$ (ng.h/mL) was calculated by multiplying the AUC_{0-t} and C_t and final division of K_{el}, area under the first moment curve $AUMC_{0-24}$ (ng.h2/mL), $AUMC_{0-\infty}$ (ng.h2/mL), mean residence time MRT of drugs were determined from plasma concentration time profile. The values are expressed in the term of mean ± standard deviation (SD). The pharmacokinetic parameters compared with single dose administration as a 2% suspension of drug with SCMC and the floating tablets in as a test in a normal Rabbits. Results were compared using paired 't' test with a probability of $P<0.05$ to be significant.[21,22]

RESULTS AND DISCUSSION

The prepared tablets of all formulations were tested weight variation they are in prescribed limits as show in table no 3. The hardness of prepared tablets was found in the range 4 to 8 kg/cm^2. The percentage friability test of tablets was within range of 0.96 to 0.99.[23] The drug content of each floating tablet was within the range of 95-101 as compare with the Indian Pharmacopoeia as show in table no 3.

Table 1: Composition of different floating tablet formulations of Apricitabine.

Ingredients (mg)		**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**	**F19**	**F20**
1	Apricitabine	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800
2	Pharmacel 101	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
3	PVPK30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
4	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Extra granular part																					
1	Gantrez AN-119		100			50	50	75	75	50	50	75	75	75	75	75	75	75	75	75	75
2	Gantrez MS-995			100		50		50		75											
3	Gantrez S-97				100		50		50		75	50	50	50	50	50	50	50	50	50	25
4	HPMC K100M											25	50			25	50	50	75	75	75
5	HPMC K15M													25	50	25	50	75	50	75	75
6	Lactose Monohydrate	95	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	35
7	Citric acid	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
9	Sodium bi carbonate	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	30
10	Magnesium strarate	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Total weight		1000	1025	1025	1025	1025	1025	1050	1050	1050	1050	1075	1100	1075	1100	1100	1150	1175	1175	1200	1200
Floating Lag Time (sec)		--	198	106	156	123	148	134	168	216	285	315	352	204	132	212	109	162	183	194	103
Floating Time		--	>10	> 10	>10	> 6	> 8	>10	>12	>8	>8	>16	>16	>24	>24	>24	>24	>24	>24	>24	>24

Table 2: Evaluated for flow property

Formulation	Angle of Repose	Bulk Density	Tapped Density	Hausner Ratio	Compressibility Index
F1	25.13	0.304	0.350	1.15	13.14
F2	26.12	0.308	0.356	1.15	13.48
F3	27.65	0.306	0.374	1.22	18.18
F4	26.85	0.303	0.395	1.33	23.29
F5	26.42	0.309	0.347	1.12	10.95
F6	25.31	0.341	0.385	1.12	11.42
F7	26.14	0.301	0.394	1.30	23.60
F8	28.31	0.308	0.354	1.14	12.99
F9	26.45	0.306	0.342	1.11	10.52
F10	23.18	0.304	0.385	1.26	21.03
F11	27.36	0.309	0.351	1.13	11.96
F12	26.85	0.306	0.375	1.22	18.4
F13	27.69	0.307	0.348	1.13	11.78
F14	27.15	0.308	0.387	1.25	20.41
F15	29.35	0.304	0.394	1.29	22.84
F16	24.36	0.315	0.368	1.16	14.40
F17	25.45	0.314	0.359	1.14	12.53
F18	27.52	0.320	0.372	1.16	13.97
F19	28.45	0.316	0.391	1.23	19.18
F20	29.32	0.304	0.348	1.14	12.64

Table 3: Hardness, Friability, Weight variation and Drug content of tablets of different formulation F1 to F20

Formulation	Hardness (Kg/cm2)	Friability (%)	Weight Variation (mg)	Drug content uniformity (%)
F1	5.3±0.15	0.96	1000±0.12	99±0.11
F2	6.3±0.17	0.98	1025±0.22	98±0.13
F3	6.3±0.21	0.99	1025±0.21	100±0.45
F4	6.8±0.12	0.97	1025±0.11	98±0.52
F5	5.1±0.03	0.99	1025±0.23	99±0.17
F6	5.6±0.23	0.97	1025±0.11	97±0.16
F7	5.8±0.12	0.95	1050±0.45	98±0.28
F8	5.8±0.42	0.97	1050±0.11	99±0.16
F9	6±0.01	0.98	1050±0.32	97±0.26
F10	5.2±0.12	0.99	1050±0.15	99±0.27
F11	5.2±0.16	0.97	1075±0.36	98±0.41
F12	5.6±0.19	0.98	1100±0.24	101±0.13
F13	5.6±0.17	0.99	1075±0.11	95±0.11
F14	6.0±0.13	0.97	1100±0.17	99±0.85
F15	6.4±0.18	0.99	1100±0.09	97±0.24
F16	7.2±0.21	0.97	1150±0.08	98±0.32
F17	6.8±0.14	0.98	1175±0.19	99±0.77
F18	6.4±0.11	0.97	1175±0.18	98±0.31
F19	6.4±0.16	0.98	1200±0.71	98±0.41
F20	6.6±0.13	0.98	1000±0.22	99±0.56

Table 4: Model dependent kinetic analysis of the dissolution profiles.

Formulation	Zero order drug Release		first order drug release		Higuchi Plot		Korsmeyer -Peppas Plot	
	r2	slope	r2	slope	r2	slope	r2	slope
F2	0.9543	0.106	0.9717	-0.111	0.9833	30.873	0.9949	0.642
F3	0.9489	0.105	0.8224	-0.147	0.9869	31.054	0.9922	0.588
F4	0.9019	0.104	0.9606	-0.124	0.9949	30.885	0.9908	0.508
F5	0.9786	0.066	0.6793	-0.26	0.9129	36.704	0.9734	0.769
F6	0.9642	0.091	0.9502	-0.097	0.9792	32.717	0.9774	0.582
F7	0.963	0.096	0.9035	-0.147	0.9727	34.035	0.9948	0.712

F8	0.9553	0.112	0.9526	-0.12	0.9552	31.893	0.9786	0.755
F9	0.9539	0.076	0.9168	-0.176	0.9902	36.007	0.9928	0.581
F10	0.931	0.089	0.8812	-0.155	0.9879	32.918	0.9543	0.471
F11	0.9724	0.256	0.9637	-0.084	0.9403	26.21	0.9753	0.813
F12	0.9228	0.157	0.9744	-0.062	0.9573	25.668	0.9814	0.837
F13	0.8768	0.223	0.9783	-0.054	0.9612	22.173	0.9601	0.756
F14	0.9051	0.251	0.9945	-0.037	0.9739	20.07	0.9742	0.751
F15	0.8952	0.214	0.9644	-0.066	0.9635	23.219	0.9673	0.806
F16	0.9823	0.263	0.9371	-0.046	0.9643	20.356	0.9923	0.728
F17	0.9462	0.262	0.996	-0.037	0.9793	19.689	0.9918	0.738
F18	0.9523	0.266	0.994	-0.034	0.9763	19.405	0.9874	0.807
F19	0.9374	0.278	0.9961	-0.03	0.9791	18.487	0.9899	0.728
F20	0.8985	0.302	0.9893	-0.026	0.9939	16.771	0.9891	0.532

Table 5: *Invivo* pharmacokinetics parameters.

Pharmacokinetic parameter	Floating tablet (f16)	Suspension 2% scmc
C_{max} (ng/ml)	1073	1417
T_{max}(h)	6	2
K_{el} (h^{-1})	0.0637	0.12913
$t_{1/2}$(h)	10.88	5.36790
$AUC_{0--24}^{(ng.h/ml)}$	15232.875	72333.95
$AUC_{0--\infty}^{(ng.h/ml)}$	19477.535	7809.670
K_a (h^{-1})	0.24675	1.49208
MRT	3.822	12.624

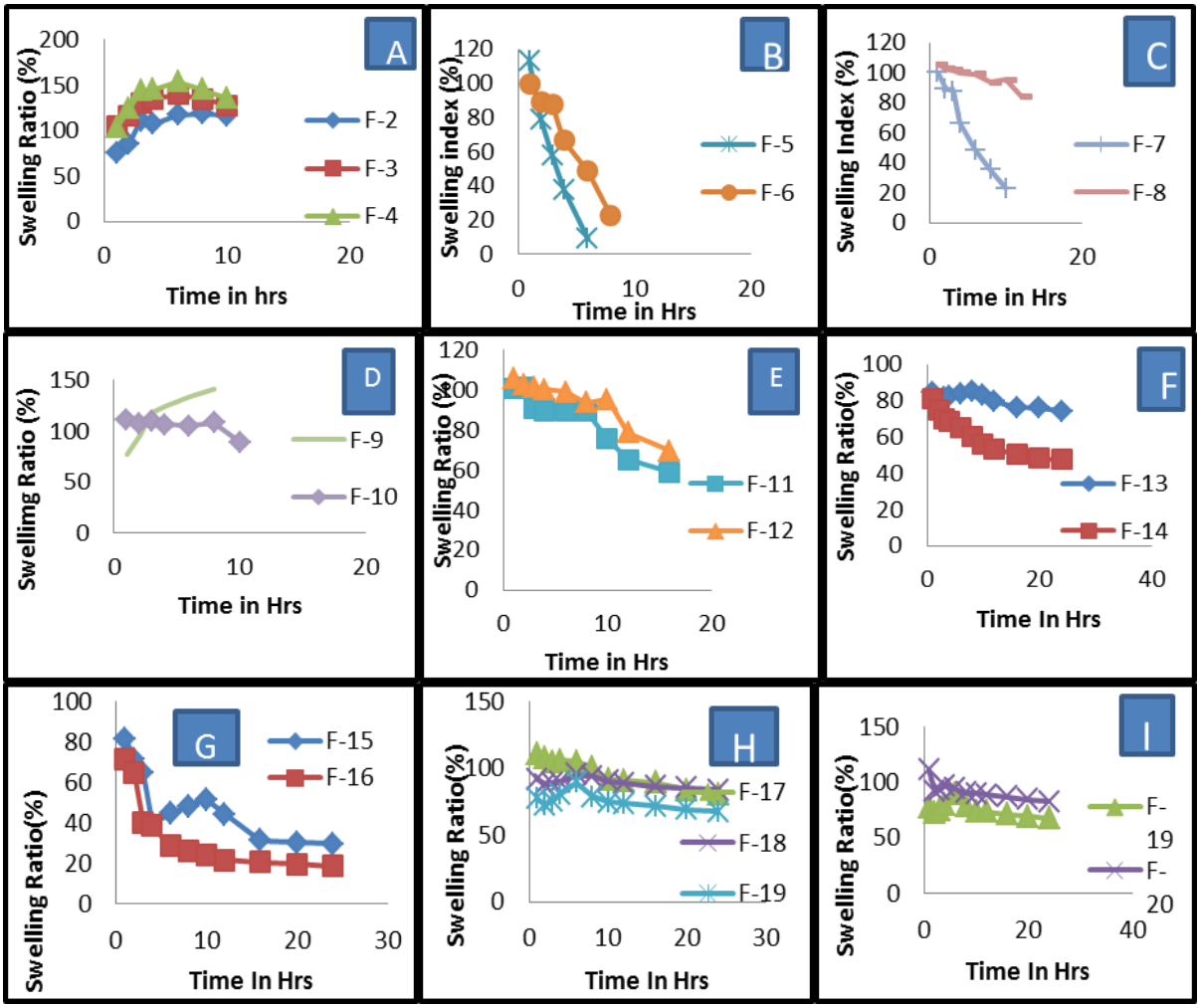


Fig. 1: Swelling studies of all formulation.

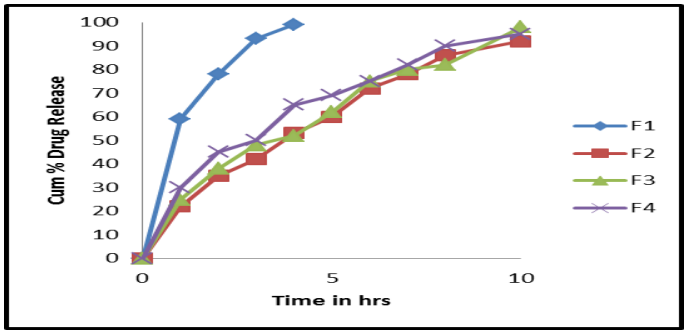


Fig. 2: *Invitro* drug release studies of F1 to F4 Formulation.

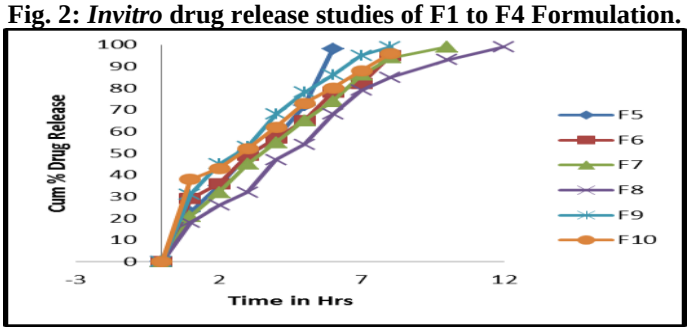


Fig. 3: *Invitro* drug release studies of F5 to F10 Formulation.

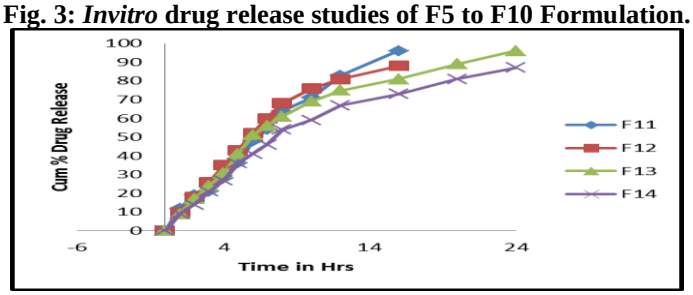


Fig. 4: *Invitro* drug release studies of F11 to F14 Formulation.

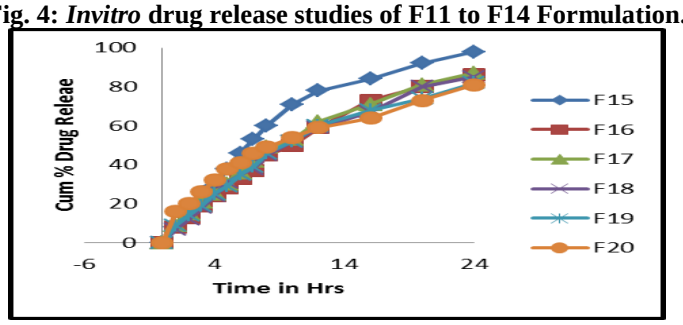
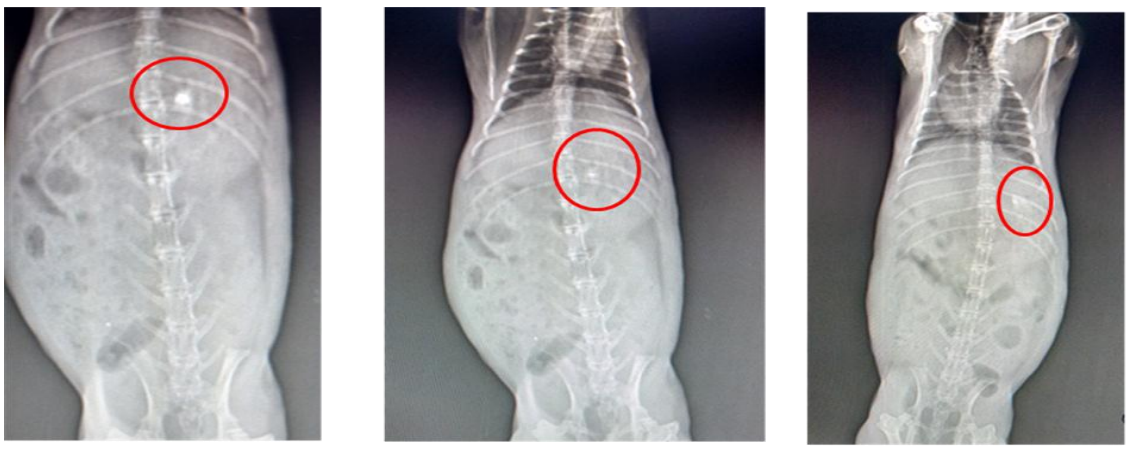


Fig. 5: *Invitro* drug release studies of F15 to F20 Formulation.



1 hrs **12hrs** **24hrs**

Fig. 6: X-ray of *invivo* studies of floating tablet of Apricitabine F-16.

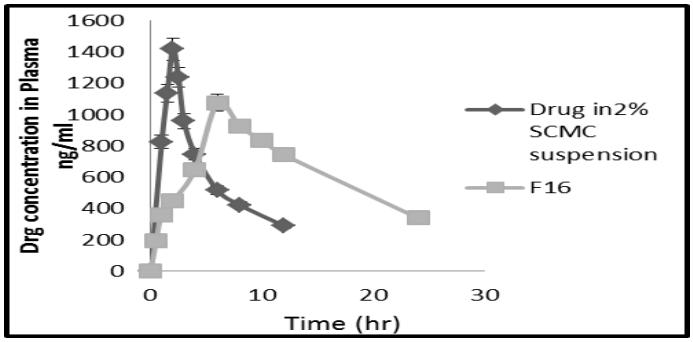


Fig. 7: *Invivo* studies of F16 and 2% suspension of Apricitabine.

In Vitro Buoyancy

The buoyancy study of tablet was tested in 0.1N Hcl solution contacting 100ml in a 100ml baker. As the tablet was placed in the solution sodium bicarbonate reacts with hydrochloric acid and carbon dioxide was evaluated due to this effect table rise up to surface of liquid. All the formulation buoyancy studies were measured in between 103sec to 352 sec. the buoyancy studies of F2, F3 and F4 was found 198,106 and 156sec. the buoyancy studies of combination of two polymers as increases the buoyancy period F5 to F10. The secondary polymer was added the buoyancy studies was increases F11 to F14. The buoyancy studies from F15 were decreases due to high hydration of tablet and show the high swelling initial.[24] The buoyancy studies were increases F16 to F19 comparing from F15 as show in table no 1.

Swelling index: The swelling properties of each formulation were studies in dissolution medium of 0.1N Hcl. The formulation F2, F3 and F4 show the swelling index was found 116.5, 127.9 and 135.4 as show in table no 1A. Which indicates drug release was high in F2 because comparing these three formulation high amount of swelling occurs and drug release also within 10hrs only. The formulation F5 to F10 showing the swelling index in that high amount of swelling occur in that F5 was show at 6hrs only and whereas F8 was 12hrs low amount swelling index was shown (fig 1B, C, D). The swelling studies of F9 randomly swelling occurs within 8hrs. F10 show the swelling up to 12 hrs. F11 and F12 has selling up to 16hrs(fig 1E).The swelling studies of F13 to F20 was slow compared to the F8 because of hydrophilic nature is introduced and drug release studies also decreases up to 24hrs (Fig 1F,G,H,I).

All the formulation drug release was sustained. The drug release studies for the formulation F2, F3 and F4 was within 10hrs as show in fig 2. The release mechanism of these three formulations was follows F1 and F3 first order and Korsmeyer -Peppas but the n value is more than 0.5 that means it follows the non fickian release and F2 was the release mechanism first order and Higuchi by considering the regression values as show in Table 4. The formulation of F5, F6, F7 and F8 show it following zero order drug release with korsmeyer –Peppas release but the drug release up to 6hrs, 8hrs,10hrs and 12hrs(fig 3) and their n value was each formulation more the 0.5 and it follows the non ficken diffusion releases.[25] The drug released from F9 and F10 show up to 8hrs release mechanism follows zero order and korsmeyer –Peppas their n values of F10 shows below 0.5 and it indicate it follows ficken release. The formulation F11 and F12 has drug release studies up to 16hrs and F11 was follows the mechanism of drug release zero order with korsmeyer-peppas whereas F12 follow the mechanism first order with kormeryer-peppas from the regression and n values it was indicated as show in table no 4. The formulation F13 to F20 drug release studies up to 20hrs(fig 4 & 5) in that F16 has excellent zero order with kormeryer-peppas mechanism release where n value is more than 0.5 it follows non-ficken diffusion release. The formulation F16 has combination of gas generating agent such as sodium bicarbonate with swelling agent such as Gantrez AN-119 and Gantrez S-97 viscosity agent HPMC K4M & K100M permit the controlled release and it occur the burst-release effect is most probably due to the rapid swelling and dissolution of the polymer of Gantrez AN - 119.

An *in vivo* X-rays study was approved by the Institutional Animal Ethical Committee (reference no. CPCSE/1657/IAEC/CMRCP/PhD-15/37). The floating property of the selected F16 tablets was studied by X-ray technique. Male rabbits with weight of 2.5 kg and the age of 12 to 14 months were chosen. The rabbits were kept in animal house under environmental condition (25°C, 12 h light and dark cycle). The rabbits were fasted for 36 h and allowed only water to it. The rabbit was administrated with best formulation (F6). The tablet was administered orally by placing them in hollow polyethylene tube. The tube was inserted into the mouth of rabbit with carefully and tablet was inserted in tube with 2ml if water to flush the tablet. X-rays were taken at interval of 1 hrs, and 24 hrs as show in fig 6. The estimation of drug from the pharmacokinetic like (CL, *V*d, *t*1:2, area under the curve (AUC)). From the graphs of plasma concentration on x-axis and time profile on y-axis of the gastro-floating tablets and 2% suspension of SCMC on albino rats are illustrated in Fig. 7 and Table 5. The graph it can conclude that C_{max} in floating tablet and 2% suspension was found to be 1073 and 1417, whereas the T_{max} was 6hrs and 2hrs, $t_{1/2}$ delayed by 10.88 hrs of F16 whereas 5.36 of 2% suspension SCMC in comparison area under the curve at 24h 15232.875 2%

suspension 72333.95, $AUC_{0-\infty}$ (ng.h/ml) was increases 7809.670 with floating tablet 19477.535.

CONCLUSION

In this research work floating matrix tablet was formulated by mixing drug with other ingredient as described above. It showed acceptable results of all tables with respect to floating lag time, total floating tiem, swelling ability, and controlled drug release rates was obtained. The best formulation F16 contain 800mg drug, Gantrez AN-119 (75mg), Gantrez S-97(50mg),HPMC K4M & K100M (50mg) and gas generating agent. The F16 formulation has buoyancy studies has 109 sec and mechanism of drug release was non-Fickian diffusion from that tablet. It indicates that water diffusion into the tablet and swelling of tablet by the polymer delay release drug. From the Invivo studies it was included that controlled releases dosage forms occurs and decreases the half live of drug.

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