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Original Research Article

FORMULATION AND EVALUATION OF ACYCLOVIR MULTIUNIT FLOATING FORMULATIONS TO INCREASE GASTRIC RETENTION BY EMPLOYING LIPOIDAL CARRIERS

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ABSTRACT

The purpose of this investigation was to formulate hydrodynamically balanced gastric retentive drug delivery system of Acyclovir. Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV). It has an elimination half life of about 2.5-3.3 hours. Non-effervescent formulations of Acyclovir were prepared with novel lipoid carriers like Gelucire 43/01, Gelucire 50/02, Compritol ATO 888, Geleol pellets by using different granulation techniques in the ratios of 1:1, 1:1.25 and 1:1.5 were compared to effervescent formulations comprising HPMC K4M, HPMC K15M, HPMC K100M. All the formulations were evaluated for Micromeritic properties, buoyancy parameters and *in vitro* drug release studies were carried out for 12 hours. The *in vitro* release data obtained was fitted to various linear and regression kinetic models to assess the release profile of the drug. Based on results obtained from the preliminary formulations, optimized formulations are selected for further studies. Short-term stability studies were done for optimized formulations. The data obtained in this study suggests that the multiunit floating formulations of Acyclovir can be successfully designed to give controlled drug delivery and improved oral bioavailability.

Key words: Acyclovir, Gelucire 43/01, Gelucire 50/02, Compritol ATO 888, Geleol Pellets.

INTRODUCTION

Retention of drug delivery system in the stomach prolongs overall gastrointestinal transit time and improves the oral bioavailability of the drugs that are having site specific absorption from the stomach or upper part of the small intestine[1]. Therefore different approaches have been proposed to retain the dosage form in the stomach including bioadhesive systems[2], swelling and expanding system[3], sedimentation[4] and floating systems[5]. Based on these approaches, floating drug delivery systems offers a simple and practical approach to achieve increased gastric residence time for control release of drugs. Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV). It has an elimination half life of about 2.5-3.3 hours and oral bioavailability is 10-20% [6].

In the present study, an attempt was made to develop gastro retentive floating drug delivery system of Acyclovir using HPMC K4M, HPMC K15M, HPMC K100M, Gelucire 43/01, Gelucire 50/02, Compritol ATO 888,Geleol pellets by wet granulation and melt extrusion techniques[8] respectively. So that to restrict the drug release preferably in upper part of intestine and to improves its bioavailability and to provide constant drug plasma levels thereby improving patient compliance[7].

OBJECTIVE

The present research work aims to develop hydrodynamically balanced non-effervescent floating dosage form, which release the drug at a rate- controlled manner by showing extended retention.

1. To carryout the Drug- Excipient compatibility studies.
2. To evaluate the drug release in developed formulation by in vitro studies and optimize the best formulation.

MATERIALS

Acyclovir was provided by Hetero drugs, Hyderabad, HPMC K4M, HPMC K15M, HPMC K100M purchased from SD Fine chemical Laboratories, Gelucire 43/01, Gelucire 50/02, Compritol ATO 888, Geleol pellets were received as gift samples from Gattefosse, Mumbai.

METHODS

1. Drug-Excipient compatibility Studies FT-IR [8]:

The infrared spectra of Acyclovir, physical mixture of drug and Excipient which were recorded between 400 to 4000 cm-1 on FTIR. The IR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer.

2. Formulation of Acyclovir Gastro retentive multi unit formulations [9]:

Acyclovir Gastro retentive multi unit formulations comprising cellulosic polymers were prepared by wet granulation technique where as the Acyclovir Gastro retentive

multi unit formulations comprising lipoidal / fatty polymers were prepared by melt granulation technique in the ratio of 1:0.5, 1:1, 1:1.5.

a) Preparation of Multi Unit GRFDDS by Wet Granulation technique:

Required amount of drug and polymer were weighed and passed through 40 # sieve separately and blended thoroughly. The blend was granulated with PVP K30 solution that was prepared by dissolving it in isopropyl alcohol. The damp mass was passed through 16 # sieve and dried at around 55 ^{o}C for about one hour.

b) Preparation of Multi Unit GRFDDS by Melt Granulation technique:

Drug and polymer were weighed according to the experimental design. Respective lipoidal polymers were melted above 5 ^{o}C of their corresponding melting points. Drug was dispersed in the polymer melt by continuous agitation and allowed to solidify at 4^{o}C. The solidified mass was passed through 16 # sieve to attain uniformed sized granules and compositions were mentioned in the tables 1, 2 and 3.

Table.1.Composition of different Multi Unit floating Acyclovir formulations F1-F7

Formula	Drug: Polymer proportion 1:1						
	F1	F2	F3	F4	F5	F6	F7
Acyclovir	200	200	200	200	200	200	200
HPMC K4 M	200	--	--	--	--	--	--
HPMC K15M	--	200	--	--	--	--	--
L HPMC K100M	--	--	200	--	--	--	--
Gelucire 43/01	--	--	--	200	--	--	--
Gelucire 50/02	--	--	--	--	200	--	--
Compritol ATO 888	--	--	--	--	--	200	--
Geleol pellets	--	--	--	--	--	--	200

Table.2.Composition of different Multi Unit floating Acyclovir formulations F8-F14

Formula	Drug: Polymer proportion 1:1.25						
	F8	F9	F10	F11	F12	F13	F14
Acyclovir	200	200	200	200	200	200	200
HPMC K4 M	250	--	--	--	--	--	--
HPMC K15M	--	250	--	--	--	--	--
HPMC K100M	--	--	250	--	--	--	--
Gelucire 43/01	--	--	--	250	--	--	--
Gelucire 50/02	--	--	--	--	250	--	--
Compritol ATO 888	--	--	--	--	--	250	--
Geleol Pellets	--	--	--	--	--	--	250

Table.3.Composition of different Multi Unit floating Acyclovir formulations F15-F21

Formula	Drug: Polymer proportion 1:1.5						
	F15	F16	F17	F18	F19	F20	F21
Acyclovir	200	200	200	200	200	200	200
HPMC K4 M	300	--	--	--	--	--	--
HPMC K15M	--	300	--	--	--	--	--
HPMC K100M	--	--	300	--	--	--	--
Gelucire 43/01	--	--	--	300	--	--	--
Gelucire 50/02	--	--	--	--	300	--	--
Compritol ATO 888	--	--	--	--	--	300	--
Geleol Pellets	--	--	--	--	--	--	300

3. Characterization of Prepared Acyclovir Gastro retentive multi unit formulations:

a) Evaluation of flow properties of granules like bulk density, tapped density, compressibility index, Hausner ratio, angle of repose [10]

b) In vitro buoyancy studies[11, 12]:

The *in vitro* buoyancy was characterized by floating lag time and total floating time. The test was performed using a USP XXIII type 2 dissolution test apparatus using 900 ml

of 0.1 N HCl at paddle rotation of 50 rpm at 37°±0.5°C. The time required for the tablet to rise to the surface of the dissolution medium and the duration of time, the tablet constantly floated on the dissolution medium were noted as floating lag time and floating time, respectively.

c) In vitro drug release studies [13]:

The *in vitro* dissolution studies of FDDS of acyclovir were carried out in USP XXIII type 2 dissolution test apparatus, employing a paddle stirrer at 50 rpm using 900 ml of 0.1 N HCl as dissolution medium. At specific time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a prefilter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37±0.5°C. The samples were analyzed for drug release by measuring the absorbance at 255 nm using UV/Vis double beam spectrophotometer after suitable dilutions.

d) Kinetic analysis of release data [14-16]:

In order to study the exact mechanism of drug release from the formulation, drug release data was analyzed according to zero order, first order, Higuchi square root, Korsmeyer- Peppas model. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test.

RESULTS AND DISCUSSION

1. Compatibility studies of Acyclovir

Acyclovir was subjected to Drug – Excipients compatibility studies with various excipients like , HPMC K4M, HPMC K15M, HPMC K100M, Gelucire 43/01, Gelucire 50/02, Compritol ATO 888, Geleol pellets. It was concluded that that there was no interaction between the drug and polymer as the principle peaks of the drug were found unaltered in the IR spectra . No prominent enthalpy changes were observed in IR Spectra.

2. Evaluation of flow properties: all the formulations showed good flow property and Carr's index. The results of angle of repose indicates good flow property of the granules and the value of Carr's compressibility index further showed support for the flow property.

3. In vitro buoyancy studies:

The results for floating time are presented in Table 7. From the study of floating properties, it was observed that the floating lag time ranges from 2 seconds to 12 minutes and remained buoyant up to more than 12 hours.

4. In vitro drug release studies:

In vitro dissolution studies of all the floating formulations of Acyclovir were carried out in 0.1N HCl. The study was performed for 12 h and cumulative drug

release was calculated at every one hour time interval. In vitro dissolution studies of all the formulations are shown in tables in 4, 5, and 6. It was observed that lipoidal carriers influences the drug release pattern. Among all the lipoidal carriers Gelucire 43/01 shows significantly higher rate and extent of drug release with less floating lag time and high buoyancy time. So F4 was selected as optimized formulation which consists of 1:0.5, drug: polymer ratio.

5. Kinetic analysis of release data:

The drug release data of optimized formulation (F4) were fitted to models representing Higuchi's, zero order, first order and Korsmeyer's- peppas equation kinetics to know the release mechanisms. The results are shown in Table 8 .In the present study, in vitro release profiles could be best expressed by Higuchi's equation as optimized formulation (F4) showed good linearity indicates that diffusion is dominant mechanism of drug release with typical zero order release.

Table.4.Cumulative Percent Drug release of Acyclovir formulations F1-F7

Time (Hours)	**Cumulative Percent Drug release F1-F7**						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
0	0	0	0	0	0	0	0
0.5	8.28± 0.32	15.28±1.03	20.31±0.23	4.01±1.34	22.23±0.62	9.05±1.36	2.06±0.38
1	10.7±0.56	27.13±0.51	25.65±0.86	9.43±0.15	38.48±0.72	18.42±1.56	10.92±0.56
1.5	25.21±2.12	39.45±0.96	36.82±0.93	19.28 ±2.32	49.59±1.49	24.85±2.23	17.21±0.79
2	48.62±1.23	62.52±0.40	48.96±0.51	26.77±0.97	69.12±2.01	38.31±0.23	31.12±0.89
3	57.83±0.25	82.73±0.23	69.6±0.26	38.66 ±0.82	78.71±0.36	51.33±0.67	47.91±1.02
4	78.59±0.29	97.82±0.25	78.28±0.36	41.15±0.21	98.73±1.20	62.69±0.79	53.64±1.26
5	90.6±0.98	---	85.34±0.47	58.57±1.13	---	77.09±0.96	68.28±1.45
6	96.32±0.56	---	99.11±0.89	63.63±0.54	---	83.85±0.57	72.28±1.29
8	---	---	---	70.89±0.96	---	96.23±0.65	84.15±0.76
10	---	---	---	82.54 ±0.85	---	---	95.12±0.82
12	---	---	---	98.26 ±0.98	---	---	---

Table.5.Cumulative Percent Drug release of Acyclovir formulations F8-F14

Time (Hours)	Cumulative Percent Drug release						
	F8	F9	F10	F11	F12	F13	F14
0	0	0	0	0	0	0	0
0.5	9.12±1.02	11.45± 0.23	6.2±0.23	2.01±1.21	28.02±0.23	8.09±1.56	14.54±0.56
1	13.34±0.32	15.43±0.53	10.56±0.69	15.23±1.14	35.1±0.56	15.23±1.23	19.28±1.23
1.5	20.58±0.46	22.15±1.98	16.11±0.96	19.86±1.34	42.34±1.23	21.19±1.56	32.06±1.58
2	32.23±1.96	27.97±0.56	26.32±0.98	21.12±0.15	47.91±1.56	30.57±0.24	48.57±1.69
3	43.47±2.03	31.84±0.36	29.22±1.03	28.42±0.97	58.23±1.48	33.24±0.56	51.71±0.69
4	55.31±1.98	33.58±0.48	38.98±1.79	32.68±0.69	62.82±1.92	44.26±1.28	62.86±0.46
5	63.33±0.89	35.57±0.56	40.13±1.07	48.24±0.28	74.34±1.23	50.38±0.98	77.91±1.82
6	71.41±0.72	38.09±2.02	47.26±0.52	53.32±1.28	82.61±0.23	61.02±0.23	83.06±1.56
8	83.86±0.58	42.12±1.29	52.31±0.84	68.61±1.74	99.28±0.98	72.09±2.23	94.51±0.75
10	92.72±0.63	58.28±1.63	68.12±1.75	72.03±0.84	----	89.58±2.56	---
12	---	66.08±1.68	72.28±0.89	74.04±0.96	---	99.22±1.29	---

Table.6.Cumulative Percent Drug release of Acyclovir formulations F15-F21

Time (Hours)	Cumulative Percent Drug release						
	F15	F16	F17	F18	F19	F20	F21
0	0	0	0	0	0	0	**0**
0.5	17.81±0.56	2.27±0.56	28.12±0.14	4.01±0.56	3.27±0.97	38.1±1.20	6.97±0.68
1	21.26±0.96	13.93±1.28	31.16±1.15	14.09±0.14	7.2±0.79	52.22±1.56	11.23±0.89
1.5	38.31±1.25	28.81±1.54	44.39±1.49	21.14±0.59	18.4±0.25	89.43±1.28	16.55±1.26
2	42.23±1.89	40.62±0.68	63.44±1.55	37.42±0.89	22.5±1.26	98.52±0.68	23.36±0.45
3	63.81±1.98	78.17±0.98	72.68±1.98	56.33±0.79	37.6±0.84	---	31.72±1.29
4	75.21±1.23	84.12±1.56	87.73±1.79	61.28±1.75	48.4±1.20	---	48.31±0.55
5	82.89±1.24	97.24±1.32	89.32±0.23	72.71±1.25	53.8±0.75	---	65.8±0.48
6	99.28±1.78	---	93.2±1.56	87.82±0.98	61.1±0.68	---	74.12±0.68
8	---	---	---	99.37±0.57	70.12±0.69	---	79.38±1.23
10	---	---	---	---	83.28±1.10	---	84.56±0.12
12	---	---	---	---	84.62±1.44	---	92.28±0.97

Table.7.In-Vitro buoyancy results of Acyclovir Formulations

Formulation Code	Buoyancy Lag time (Min)	Duration of Floating (Hrs)	Formulation Code	Buoyancy Lag time (Min)	Duration of Floating (Hrs)
F1	6	5	**F12**	2	11
F2	2	>12	**F13**	1.2	6
F3	1	8	**F14**	1	>12
F4	10 sec	>12	**F15**	2 Sec	>12
F5	5	9	**F16**	2	>12
F6	2	5	**F17**	2.3	5
F7	40 sec	>12	**F18**	1	10
F8	3	10	**F19**	12	8
F9	4	8	**F20**	2	7
F10	1	7	**F21**	1.8	6
F11	4.2	>12			

Table.8.Correlation Coefficient (r) values and Release kinetics of Acyclovir Multi Unit GFDDS

Formulation	Zero order	First order	Higuchi	Erosion	Peppas Equation	
	r	r	r	r	r	n
F1	0.962	0.955	0.918	0.963	0.95	1.203
F2	0.977	0.907	0.924	0.979	0.987	1.457
F3	0.909	0.991	0.974	0.953	0.98	1.471
F4	0.938	0.446	0.965	0.948	0.962	1.027
F5	0.913	0.839	0.972	0.949	0.988	1.576
F6	0.942	0.934	0.963	0.961	0.987	1.259
F7	0.924	0.965	0.54	0.937	0.919	0.953
F8	0.921	0.982	0.97	0.95	0.982	1.199
F9	0.746	0.942	0.961	0.911	0.965	1.221
F10	0.901	0.981	0.974	0.949	0.976	1.071
F11	0.904	0.97	0.959	0.935	0.88	0.952
F12	0.709	0.764	0.973	0.912	0.988	1.555
F13	0.952	0.801	0.968	0.979	0.992	1.178
F14	0.873	0.964	0.973	0.932	0.969	1.37
F15	0.945	0.756	0.963	0.969	0.973	1.421
F16	0.96	0.931	0.88	0.964	0.939	1.035
F17	0.737	0.979	0.972	0.875	0.948	1.576
F18	0.954	0.835	0.944	0.959	0.954	1.098
F19	0.906	0.989	0.964	0.931	0.948	0.963
F20	0.955	0.913	0.949	0.961	0.946	1.778
F21	0.89	0.982	0.946	0.915	0.966	1.102

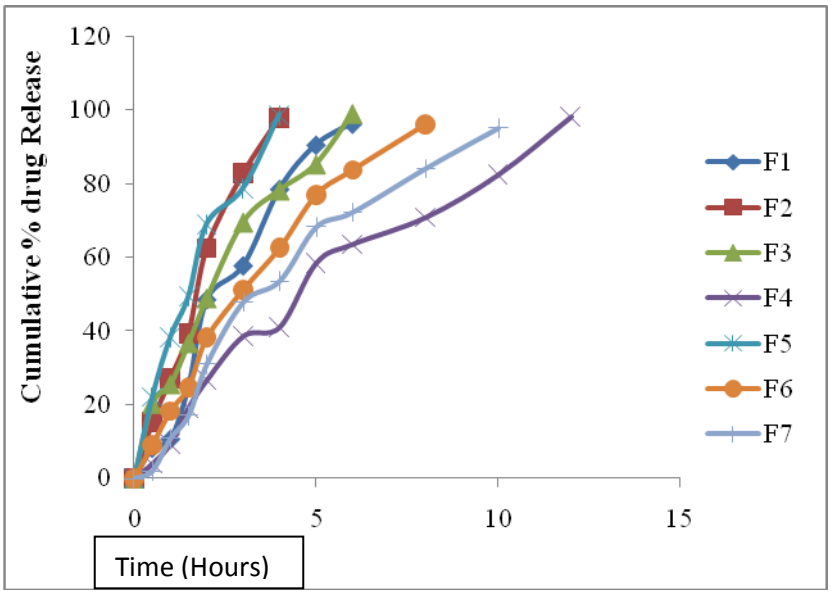

Fig.1.Cumulative Percent Drug release of Acyclovir formulations F1-F7

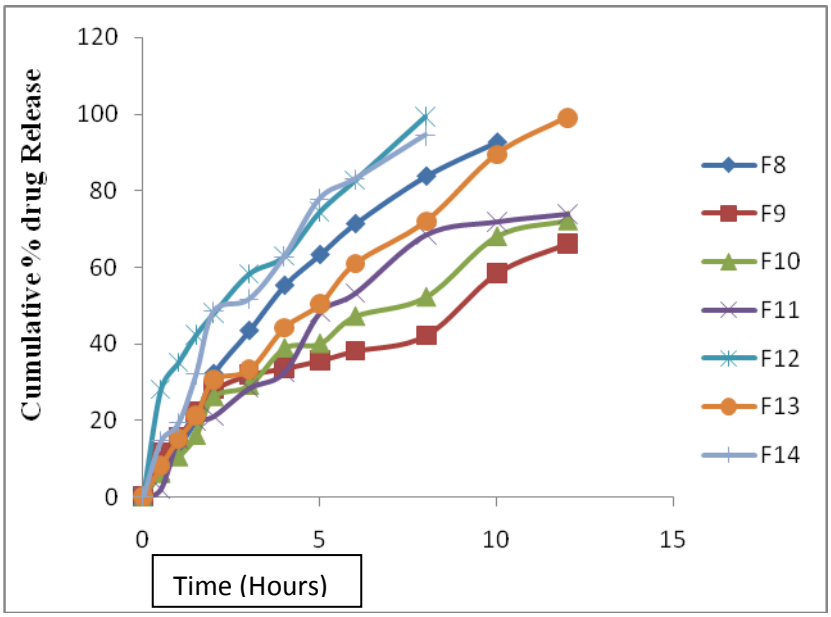

Fig.2.Cumulative Percent Drug release of Acyclovir formulations F8-F14

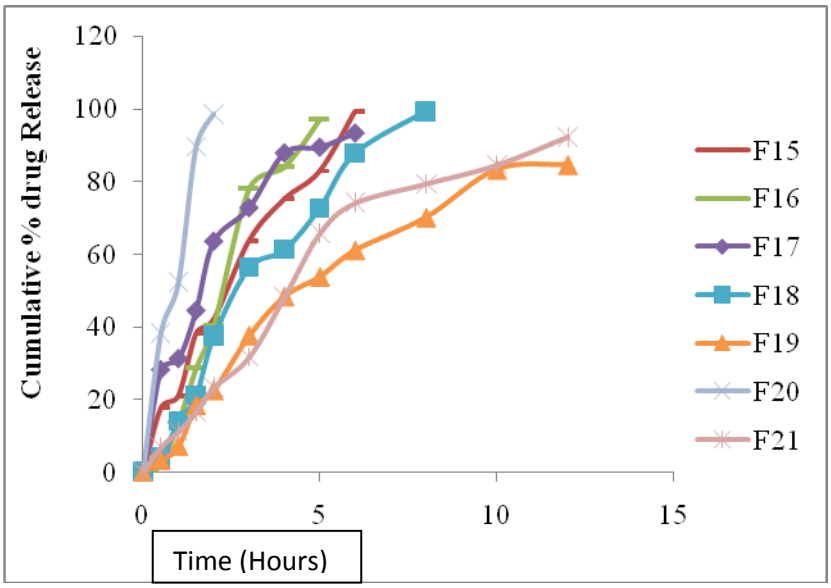

Fig.3.Cumulative Percent Drug release of Acyclovir formulations F15-F21

CONCLUSION

The in vitro drug release studies of the prepared multi unit GFDDS were studied separately according to their proportions (1:1, 1:1.25 and 1:1.5) using 0.1N Hcl as medium. Formulation F4 prepared with low concentration of Gelucire 43/01 (1:1 ratio) had retarded the release of Acyclovir in a rate controlled manner up to desired 12 hours. In the present work floating formulations of Acyclovir are formulated to provide sustained release of drug with the aim of providing an effective and safe therapy for viral infections with a reduced dose, increased bioavailability, and Suitable drug release pattern for several hours by reduced length of treatment.

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