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Formulation and evaluation of floating matrix tablets of acyclovir

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ABSTRACT:

In the present research work the gastro retentive floating matrix tablets of Acyclovir were prepared by using various hydrophilic polymers. Acyclovir is a Nucleoside analog reverse-transcriptase inhibitor (NARTI) active against HIV. It has low bioavailability of 15-30% and has a short half life of 3 hours, thus it is formulated as floating tablet by which bioavailability increases and the half life of drug is increased. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers. The formulation blend was subjected to various preformulation studies, results of all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations prepared, sodium alginate retarded the drug release in the concentration of 150 mg showed required release pattern i.e., retarded the drug release upto 12 hours and showed maximum of 99.52 % in 12 hours (Formulation F5) with good floating time and buoyancy lag time. Increase in polymer concentration retarded the drug release for more than 12 hours. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed zero order kinetics and Peppas mechanism of drug release.

Keywords: Acyclovir, Methocel K100M, Floating tablets, Sodium alginate, Buoyancy lag time.

INTRODUCTION

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient [1].

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a

drug to a specific region within the GI tract for either local or systemic action.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (solid dispersion or liquid), must be developed within the intrinsic characteristics of gastro intestinal (GI) physiology. Therefore the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of (i) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug (ii) the anatomic and physiologic characteristics of the gastrointestinal tract and (iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed [2].

Conventional oral controlled dosage forms suffer from mainly two adversities. The short gastric retention time (GRT) and unpredictable gastric emptying time (GET). A relatively brief GI transit time of most drug products impedes the formulation of single daily dosage forms.

Altering the gastric emptying can overwhelm these problems. Therefore it is desirable, to formulate a controlled release dosage form that gives an extended GI residence time [3, 4].

In order to optimize the therapy, research efforts have been focused on the development of oral sustained release (SR) preparations as well as controlled release gastro retentive dosage forms. A conventional oral SR formulation releases most of the drug content at colon, thus requiring that the drug will be absorbed from colon.

Acyclovir is a potent antiviral drug with low toxicity. Acyclovir is a Nucleoside analog reverse-transcriptase inhibitor (NARTI) active against HIV. It is slowly and scarcely absorbed from the gastrointestinal tract when administered orally and has maximum absorption in stomach and upper part of small intestine. It has low bioavailability of 15-30% and has a short half life of 3hours [5, 6].

The above drawbacks provide a rationale for developing Acyclovir as a gastro retentive dosage form, which can be retained in the stomach and produces a constant input of drug to the absorption site. This improves the bioavailability of the drug, reduces frequency of dosing, thus minimizes side effects and enhances patient compliance. The present study is a systematic approach for the development of Intragastric Buoyant tablets of Acyclovir with a view to enhance its oral bioavailability and efficacy.

MATERIALS AND METHODS

Materials: Acyclovir was obtained from Sura labs Hyderabad. Methocel K 100M, guar gum, sodium alginate, sodium bicarbonate, magnesium stearate, micro crystalline cellulose, talc were purchased from Merck Specialties Pvt Ltd, Mumbai, India.

Methods:

Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any

spectrum changes.

Optimization of Sodium bicarbonate concentration:

Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate (as mentioned in Table 1) were taken and tablets were prepared by direct compression method. Floating lag time and floating duration were observed for the prepared trail formulations. Based on the floating lag time and floating duration the concentration of sodium bicarbonate was optimised and proceeded for further formulations.

Formulation development of Tablets:

All the formulations were prepared by direct compression. The compression of different formulations is given in Table 2. Acyclovir and all other ingredients were individually passed through sieve no $\neq$ 60 and were mixed thoroughly by triturating up to 15 min. The powder mixture was then lubricated with talc. This powder blend is subjected to compression after making up the total weight of individual tablet to 500mg.

Evaluation methods:

Precompression evaluation [7]:

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia are Bulk density, tapped density, compressibility index, hausner's ratio and angle of repose.

Post compression evaluation:

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. The thickness of the tablets was determined by using vernier callipers.

Table. 1: Optimization sodium bicarbonate concentration

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Acyclovir	100	100	100	100	100	100	100	100	100
Guar gum	100	150	200	-	-	-	-	-	-
Sodium alginate	-	-	-	100	150	200	-	-	-
Methocel K100 M	-	-	-	-	-	-	100	150	200
Sodium bicarbonate	75	75	75	75	75	75	75	75	75
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
MCC	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total weight (mg)	500	500	500	500	500	500	500	500	500

Table. 2: Formulation composition for floating tablets

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10%
80-250	130-324	7.5%
More than	More than 324	5%

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the Table 3 and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = \frac{(\text{Individual weight} - \text{Average weight})}{\text{Average weight}} \times 100$$

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{ Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Where, W_1 = initial weight, W_2 = final weight of tablets.

Determination of drug content:

Ten tablets were taken and finely powdered. powder equivalent to one tablet weight of acyclovir were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer at 252nm and drug concentration was calculated [8].

In-vitro Buoyancy studies:

The *in-vitro* buoyancy was determined by floating lag time and total floating time. The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT) [9, 10].

In vitro drug release studies

900ml Of 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temperature of $37^\circ\text{C} \pm 0.5^\circ\text{C}$. Tablet was placed in the vessel and the vessel was covered. The test was carried out for 12 hours in 0.1 N HCl as dissolution medium at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml fresh receptor fluid was replaced. Suitable dilutions were done with

Table. 3: Pharmacopoeial specifications for tablet weight variation

Formulation Code	Angle of Repose(θ)	Bulk density (gm/cm ³)	Tapped density (gm/cm ³)	Carr's index (%)	Hausner's Ratio
F1	27.91	0.45	0.55	18.18	1.22
F2	28.23	0.45	0.54	16.66	1.20
F3	25.34	0.51	0.62	17.74	1.21
F4	26.71	0.46	0.54	14.81	1.17
F5	28.34	0.50	0.58	13.79	1.16
F6	27.23	0.48	0.55	12.72	1.14
F7	29.34	0.49	0.57	14.03	1.16
F8	26.78	0.44	0.52	15.38	1.18
F9	26.78	0.41	0.50	18	1.21

receptor fluid and analyzed by spectrophotometrically at 252 nm using UV-spectrophotometer [11].

Application of Release Rate Kinetics to Dissolution Data:

To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi and Korsmeyer-Peppas release model [12-14].

RESULTS AND DISCUSSION

Drug-excipient compatibility study:

The FTIR spectra of pure drug and drug along with polymers were obtained and given in figure 1 and 2. From the spectra it was found that there was no appearance or disappearance of any characteristics peaks. This shows that there is no chemical interaction between the drug and the polymers used in the tablets.

Precompression parameters of powder blend

Powder blend of tablet formulations was subjected to various pre-compression parameters and the results are presented in Table 4. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.41 to 0.51 (gm/cm³), the tapped density of all the formulations was found to be in the range of 0.50 to 0.62 (gm/cm³). The compressibility index of all the formulations was found to be ranging from 13.79 to 18 which show that the powder has good flow properties. All the formulations have shown the hausner's ratio ranging between 1.20 to 1.22 indicating the powder has good flow properties.

Optimization of sodium bicarbonate concentration:

Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation

Fig. 1: FT-TR Spectrum of Acyclovir pure drug

Fig. 2: FTIR of Drug along with excipients

Table. 4: Pre compression parameters of powder blend

Formulation code	Weight variation (mg)	Hardness (kg/cm ²)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)
F1	512.5	4.5	0.42	4.8	99.76	4.0
F2	505.4	4.2	0.48	4.9	98.45	4.2
F3	498.6	4.4	0.52	4.7	99.34	4.5
F4	510.6	4.5	0.54	4.6	98.87	4.1
F5	509.4	4.4	0.51	4.7	99.14	4.0
F6	510.7	4.2	0.55	4.5	99.56	4.4
F7	502.3	4.1	0.53	4.4	98.42	4.5
F8	501.2	4.3	0.50	4.7	98.65	4.6
F9	498.3	4.5	0.56	4.6	99.12	4.7

Containing sodium bicarbonate in 75mg concentration showed less floating lag time of 4 min and the tablet was in floating condition for more than 12 hours.

Post compression parameters:

Tablet quality control tests such as weight variation, hardness, friability, thickness, and drug release studies in different media were performed on the tablets and results are mentioned in the Table 5. All the parameters were found to be within limits. The floating lag time of the formulations was found to be in the range of 4-7 mins and all the tablets remained floating for more than 12 hours.

In-vitro dissolution study:

The results of in-vitro dissolution profile are given in the Tables 6, 7 and figures 3-5.

From the released data it was evident that the formulations prepared with guar gum as polymer, in lower concentration the formulations were unable to retard the drug release up to desired time period i.e., 12 hours. By increase the concentration of 200mg the polymer retard the drug release upto 12 hours and showed maximum drug release (F3 formulation drug release 98.54%).

The formulations prepared with sodium alginate retarded the drug release in the concentration of 150 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 99.52 % in 12 hours (Formulation F5) with good floating lag time and floating buoyancy time. Increase

Table. 5: Post compression parameters of the prepared tablets

Time (hr)	Cumulative % drug released		
	F1	F2	F3
0	0	0	0
0.5	25.73	20.52	18.53
1	57.23	30.47	25.97
2	82.9	45.93	30.89
3	90.873	54.85	38.7
4	99.873	68.54	44.38
5	-	73.55	50.2
6	-	88.6	58.06
7	-	97.54	64.52
8	-	-	72.88
9	-	-	79.6
10	-	-	84.09
11	-	-	90.52
12	-	-	98.54

Table. 7: Release data of Acyclovir tablets containing Methocel K100M

Time (hr)	Cumulative % drug released		
	F7	F8	F9
0	0	0	0
0.5	17.81	14.89	10.21
1	28.02	20.04	16.87
2	36.70	25.43	22.19
3	44.32	31.65	30.66
4	50.25	37.18	34.32
5	56.28	43.81	39.06
6	62.92	50.89	43.13
7	69.08	58.53	49.63
8	74.44	64.43	56.71
9	79.22	70.83	61.34
10	84.90	78.98	65.27
11	89.83	85.52	69.86
12	94.90	90.65	74.97

Table. 6: Release data of Acyclovir tablets containing guar gum

Time (hr)	Cumulative % drug released		
	F4	F5	F6
0	0	0	0
0.5	18.45	15.42	10.62
1	36.26	22.73	17.86
2	52.16	30.63	26.35
3	70.01	37.04	31.45
4	87.26	43.25	37.80
5	93.10	51.33	45.25
6	-	59.41	50.24
7	-	65.84	56.73
8	-	72.80	61.34
9	-	78.43	68.52
10	-	84.26	72.17
11	-	90.24	78.75
12	-	99.52	86.33

Table. 8: Release kinetics data for the optimized formulation

	ZERO	HIGUCHI	PEPPAS	FIRST
	Q Vs T	Q Vs $\sqrt{T}$	Log C Vs Log T	Log % Remain Vs T
Slope	6.998	29.92	0.580	-0.0127
Intercept	15.50	-11.2064	1.331	2.207
R ²	0.996	0.979	0.988	0.668

Fig. 3: Release profile of Acyclovir floating tablets containing guar gum **Fig. 4:** Release profile of Acyclovir floating tablets containing sodium alginate

Fig. 5: Release profile of Acyclovir floating tablets containing Methocel K100M

Fig.6: Zero order plot for the optimized formulation

Fig.7: First order plot for the optimized formulation

Fig.8: Higuchi plot for the optimized formulation

Fig.9: Peppas plot for the optimized formulation

the polymer concentration retard the drug release more than 12 hours.

The formulations prepared with methocel K100M showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

Based on dissolution study, formulation prepared with sodium alginate showed good release in low concentration i.e., 150 mg. So F5 formulation was taken as optimized formula.

Release Kinetics:

The mechanism of drug release from the optimized formulation was determined by using the drug release data and its results are given in Table 9 and represented graphically in Figures 6-9. The drug release data was fitted into various models and the mechanism of drug release was found to be by non fickian diffusion based on the slope value obtained in Krosmeier Peppas model.

CONCLUSION

The floating tablets of acyclovir were successfully prepared by direct compression method by using polymers such as Methocel, Sodium alginate and guar gum. The prepared formulations have shown a low floating lag time of 4-7 mins, thus bringing the formulations onto the top of the gastric contents in short time. And the tablets remained floating for more than 12 hours in the gastric region. Of all the formulations developed, formulation containing sodium alginate has shown the desired drug release and thus helps in increasing the bioavailability of acyclovir. As the drug is released in a controlled fashion the half life of the drug is enhanced and thus floating tablets were found to reduce frequency of dosing, minimizes side effects and enhances patient compliance.

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