Research Article

Formulation, Characterisation and Evaluation of Controlled Release Matrix Tablets of A Model Antiviral Drug

Dr. Jamakandi V G*, Shivanand S G
Department of Pharmaceutics, KLE University's College of Pharmacy, Hubli, Karnataka, India.
***Corresponding author's E-mail:** vilasj@rediffmail.com

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ABSTRACT

The objective of the study was to formulate and evaluate orally administered controlled release matrix tablets of acyclovir to improve patient compliance, lessen frequency of administration, and increase therapeutic efficacy. The formulations (F1–F8) were prepared by direct compression technique using different hydrophilic polymers such as hydroxypropyl methylcellulose K15, hydroxypropyl methylcellulose K100, eudragit RSPO, and ethyl cellulose. The compressed matrix tablets were evaluated for precompression parameters such as thickness, diameter, friability, hardness, weight variation, drug content, *in-vitro* dissolution study and release kinetics. The promised formulation elected based on the precompression parameters, in-vitro studies and release kinetics was further subjected to swelling index and stability studies by standard procedure. Mathematical analysis of release kinetics specified that the matrix tablets followed diffusion mechanism followed by non-Fickian transport. The results obtained from in-vitro studies showed that formulation F4 with 200 mg of hydroxypropyl methylcellulose K100 exhibited better drug release compared to other formulations. Optimized F4 formulation did not show significant difference in color, hardness, swelling index, and release data.

Keywords: Acyclovir, Matrix tablets, Controlled release, HPMC K100, HPMC K15.

INTRODUCTION

Oral route is the most popular and preferred route of drug administration. It is the utmost popular and extensively accepted route of drug delivery for its advantages such as pain-free, self-medication, ease of administration, patient compliance, accurate dosage, and cost-effectiveness. Even though the conventional route has a lot of advantages, drugs that have low half-life (<6 h) and chronic diseases that require long-term drug therapy, conventional medications should be given in multiple doses, which results in patient incompliance and adverse effects.[1, 2] This could be resolved by designing controlled release (CR) drug delivery systems.

A CR formulation delivers the medicament systemically or locally at a predetermined rate for a specified period. The CR tablets offer advantages such as improves patient compliance, reduced dose levels and adverse side effects, maintain therapeutic drug concentration, and increase safety-margin for very high-potency drugs.[3] Hydrophilic matrix systems are the most usually used means for oral CR drug delivery, as they can attain desirable drug profile, broad regulatory acceptance, ease of manufacturing, scale-up, and process validation.[4, 5] The mechanism of drug release from hydrophilic matrix occurs either by dissolution, erosion or by diffusion.[6]

Acyclovir, a guanosine analog, is a potent antiviral drug most commonly used in the treatment of herpes simplex, herpes zoster (shingles), and varicella zoster (chickenpox) infections.[7] The highly selective antiviral action of acyclovir causes termination of the deoxyribonucleic acid (DNA) chain and leads to irreversible inactivation of viral DNA polymerase. Conventional acyclovir tablets have major hitches such as short biological half-life (2.5 h), narrow absorption window in gastrointestinal tract, requirement of frequent administration i.e. five times a day based upon the type of infection. Hence, acyclovir was chosen as an ideal candidate for the fabrication of CR matrix type dosage forms to overcome patient incompliance, adverse side effects, dosing frequencies, and to maintain plasma drug concentrations.[8]

The rationale of the current investigation was focused on to formulate and evaluate CR matrix tablet of acyclovir by employing different polymers such as hydroxypropyl methylcellulose (HPMC) of grades K15, K100, eudragit RSPO and ethyl cellulose, using direct compression technique.

MATERIALS AND METHODS

The active pharmaceutical ingredient acyclovir was purchased from Strides Arcolab laboratories (Bangalore). The polymers—HPMC K15 and HPMC K100 from HiMedia (Mumbai); eudragit RSPO from Evonik Roehm, ethyl cellulose from Thomas Baker. The other excipients such as lactose, talc, and magnesium stearate were from SD Fine Chemicals Limited (Mumbai).

Fourier transform infrared studies

Fourier transform infrared (FTIR) spectroscopy was done to detect any possible interaction between the drug and the excipients. Pure drug, acyclovir, was mixed with the polymers in the ratio of 1:1, filled in the vials, labelled, and stored. Then, the prepared sample was taken and exposed to the infrared (IR) beam and spectra were

recorded in the range of 400–4000 cm^{-1}. The spectrum obtained was interpreted with the standard spectra to determine point-point interactions.

Method of preparation of matrix tablets

CR matrix tablets of acyclovir were formulated by direct compression method on rotary tablet compression machine (Rimek tablet punching machine, Minipress I) equipped with 12.5-mm punches to a hardness of 5–7 kg/cm^2. The details of the composition of each formulation are shown in Table 1. The polymers HPMC K15, HPMC K100, eudragit RSPO, and ethyl cellulose were used as a rate-retarding material. Drug of required quantity was weighed accurately; polymers were mixed thoroughly using mortar and pestle in geometric proportion and then lactose is blended thoroughly. Magnesium stearate was added to the blend as a lubricant and talc was added as a glidant. Average weight of the tablet (500 mg) was kept constant. All the formulated tablets were ensconced in an airtight container at room temperature for further studies.[9]

Table 1: Composition of formulations F1 to F8

Ingredients	Formulation codes (mg)							
	F1	F2	F3	F4	F5	F6	F7	F8
Acyclovir	200	200	200	200	200	200	200	200
HPMC K15M	150	200	–	–	–	–	–	–
HPMC K100M	–	–	150	200	–	–	–	–
Eudragit RS PO	–	–	–	–	150	200	–	–
Ethylcellulose	–	–	–	–	–	–	150	200
Lactose	135	85	135	85	135	85	135	85
Magnesium stearate	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5
Total weight (mg)	500	500	500	500	500	500	500	500

HPMC: Hydroxypropyl methylcellulose

Evaluation of post-compression parameters

Appearance

Ten tablets from each batch were chosen arbitrarily and their colors were compared visually.[10]

Dimensions

Diameter and thickness of each matrix tablet was evaluated using digital vernier caliper. Five tablets from each batch were picked arbitrarily and measured individually.[11, 12]

Hardness

From each batch, three tablets were chosen randomly and hardness was evaluated using Monsanto hardness tester.[13]

Weight variation test

Twenty tablets were picked arbitrarily from each batch and weighed, the average weight was calculated and were weighed individually to calculate the standard deviation.[14]

Friability test

Variability of matrix tablets was assessed by Roche friabilator. A total of 20 tablets picked arbitrarily were weighed and transferred into the friabilator and rotated for 4 min at 25 rpm. After a specific period, the tablets were dedusted and reweighed.[15, 16] The percentage friability was then assessed by the below formula:

$$\%\ Friability = \frac{Initial\ weight - Final\ weight}{initial\ weight} \times 100$$

A loss of <1 % in weight is usually considered acceptable.

Drug content uniformity

Five tablets were chosen randomly and powdered. The quantity equivalent to 100 mg of acyclovir was weighed and dissolved in 50 mL of 6.8 pH phosphate buffer. The rest volume was made up to 100 mL with pH 6.8 phosphate buffer stirred for 5 min, and filtered. From the stock solution, 10-mL aliquot was taken into 100-mL volumetric flask and volume was made with phosphate buffer. From this, 1 mL was pipetted into 10-mL volumetric flask and the volume was made up with buffer. The absorbance of the resultant was measured at 253 nm against pH 6.8 phosphate buffer as reference blank. Then, the content uniformity was calculated.[16, 17]

In-vitro dissolution studies

The in-vitro drug release was assessed using standard USP (United States Pharmacopoeia) Apparatus-II (paddle type)

by taking 900 mL of 0.1 N HCL for first 2 h and phosphate buffer of pH 6.8 for next 10 h. The temperature of the medium was maintained at 37 ± 0.5ºC. The rotating speed of the basket was maintained at 50 rpm. At fixed time intervals, an aliquot of 1 mL was withdrawn and made up to 25 mL with the same media mentioned above. The absorbance was determined spectrophotometrically in a Shimadzu ultraviolet-visible spectrophotometer at 253 nm. After each withdrawal, 1 mL of dissolution media was replaced to maintain the sink conditions. The dissolution studies were performed for 12 h and the cumulative percentage of drug released from the tablets was calculated and plotted against time.[18]

Release kinetics

To analyze the release mechanism and release rate kinetics of the formulations, the data attained were fitted into kinetic models— zero order, first order, Higuchi matrix, Hixon Crowell, and korsmeyer-Peppas model, using PSP-DISSO-v2 software. Based on the *R*-value attained, the best-fit model was selected.[19]

Determination of eroding behavior for optimized formulation or swelling index

It is conducted to determine the effect of swelling and erosion behavior on the drug release and also to evaluate the influence of polymer viscosity on swelling and erosion. Matrix tablets were taken into the dissolution apparatus containing phosphate buffer (pH 6.8) maintained at room temperature up to 6 h. The tablets were taken out using a basket and swollen weight of each tablet was assessed. To know the matrix erosion, swollen tablets were properly dried in a vacuum oven at 45°C until it attains constant weight.[20] The swelling index was calculated using the following equation

$$Swelling\ index = \frac{final\ weight - initial\ weight}{initial\ weight} \times 100$$

Accelerated stability studies for the optimized formulation:

Stability of the optimized matrix tablet was determined in specific time. The study was conducted as per ICH (International Conference on Harmonisation) guidelines, at 40 ± 2^0C/75 ± 5% relative humidity. After 1 month, the tablet was evaluated for physical characteristics, swelling index and percentage cumulative drug release.[21]

RESULTS AND DISCUSSION

Oral drug administration, one of the utmost cutting edge zones of drug delivery system, faces drawbacks such as frequency of administration and decreased therapeutic efficacy. Hence, in the current investigation, an attempt has been made to fabricate and evaluate orally administered CR matrix tablets of acyclovir to overcome the above challenges. The tablets (F1–F8) were prepared by direct compression technique using different hydrophilic polymers such as HPMC K15, HPMC K100, eudragit RSPO, and ethyl cellulose.

Fourier transform infrared spectroscopic

The characteristic peaks obtained for acyclovir and physical mixture (combination of drug and polymers) are presented in Table 2. The absorption peaks attained from the physical mixture disclosed that neither disappearance nor significant shift of the characteristic peaks were observed in comparison to acyclovir, which indicates that there was no mixed interaction between the acyclovir and polymers.

Table 2: Data obtained from compatibility study of drug and polymers by FTIR spectroscopy

Sample content	Important IR spectral peaks of different groups, wave length in cm^{-1}					
	N-H Stretch	O-H Stretch	C-H Stretch	N-H Bend	C-H Bend	C-N Amines
Acyclovir	3244.76	-	3078.02	1634.56	-	1323.49
Acyclovir + HPMC K15m	3308.95	-	2936.06	1637.14	1448.21	1384.97
Acyclovir + HPMC K100M	3308.77	3456.28	2937.78	1636.73	1444.90	1386.68
Acyclovir + Eudragit RSPO	3309.35	-	2937.48	1689.55	1493.84	1386.92
Acyclovir + Ethylcellulose	3309.35	3343.46	2937.0	1689.68	1449.91	1386.92

Evaluation of matrix tablets

Physiochemical evaluation

The formulated matrix tablets were white and odorless (Table 3). The results of preliminary characterization parameters were in the range of 12.6±0.03–12.7±0.03 mm in diameter, 3.4±0.01–3.6±0.03 mm in thickness, 6.0±0.312–7.2±0.419 kg/cm^2 hardness, (500.66 ± 0.8–504.41 ± 2.6 mg percentage weight variation, 0.262–0.92 % friability, and drug content uniformity of 96.18–98.93 %, respectively. Observation of all these parameters stated that the values were within the specified US pharmacopoeial limits for all the eight formulations. All the values are shown in Table 4.

Table 3: Organoleptic properties of prepared tablets

Formulation code	Colour	Odour	Formulation code	Colour	Odour
F1	White	Odourless	**F5**	White	Odourless
F2	White	Odourless	**F6**	White	Odourless
F3	White	Odourless	**F7**	White	Odourless
F4	White	Odourless	**F8**	White	Odourless

Table 4: Evaluation of Post-Compression parameters

Formulation code	Thickness ±S.D (mm) n=3	Diameter ±S.D (mm) n=3	Hardness ± S.D (kg/cm^2) n=3	Average weight Variation (mg) n=10	Friability (%)	Drug Content (%)
F1	3.4±0.01	12.7±0.03	6.9±0.475	502.33 ± 1.4	0.271	98.13
F2	3.6±0.03	12.6±0.03	7.1±0.422	500.66 ± 0.8	0.92	97.33
F3	3.4±0.01	12.6±0.02	6.5±0.482	501.33 ± 1.2	0.262	98.85
F4	3.5±0.02	12.6±0.03	7.2±0.419	503.33 ± 2.0	0.325	98.93
F5	3.5±0.02	12.7±0.02	6.2±0.493	504.41 ± 2.6	0.345	96.18
F6	3.5±0.02	12.6±0.03	6.0±0.312	502.66 ± 1.6	0.440	97.55
F7	3.6±0.03	12.6±0.03	7.0±0.411	502.59 ± 2.4	0.475	96.28
F8	3.6±0.03	12.6±0.03	6.8±0.356	501.16 ± 1.4	0.593	98.53

Release Studies

The in-vitro drug release of eight formulations of matrix tablets is represented in Table 5. Of all the formulations, formulation F4 with polymer 200 mg of HPMC K100M exhibited maximum drug release (97.41%) at the end of 12 h. The release profiles of the formulations revealed that the drug release of the matrix tablets mainly dependent on the concentration of nature and quantity of the polymers. The release data of all the formulations was in the following order:

F4 > F8 > F3 > F7 > F6 > F2 > F5 > F1

Table 5: *In-vitro* drug release profile of Formulation F1-F8

Time (h)	%CDR							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0	0	0	0	0	0	0	0
0.5	0.11	0.37	1.23	0.84	1.01	0.56	0.11	1.01
1	4.50	4.83	5.29	6.41	5.06	5.29	4.73	5.96
2	13.17	14.41	15.09	16.77	13.51	16.77	14.86	15.76
3	22.63	23.76	25.0	26.80	23.08	24.21	23.98	25.90
4	31.76	33.44	35.02	37.16	32.66	32.88	33.89	36.49
5	41.33	41.33	47.75	47.30	41.63	42.57	43.47	46.96
6	48.65	51.24	55.18	57.54	50.11	51.46	51.69	56.64
7	57.54	59.46	66.32	68.36	59.01	60.81	61.37	65.77
8	64.87	71.17	77.26	78.27	67.91	70.50	71.40	75.45
11	73.34	77.71	84.40	88.52	76.81	79.17	80.07	84.57
12	81.54	86.94	91.33	97.41	85.70	88.52	89.19	94.60

%CDR: Controlled drug release

Release kinetics

The release data obtained from different kinetics treatments showed Korsmeyer–Peppas as the best fitting model (Table 6). From the Krosmeyers-Peppas equation drug release at time 't', diffusion coefficient (n) and release rate constant (k) were calculated. These results obtained indicated that, the release mechanism for acyclovir is by diffusion mechanism followed by non-Fickian transport. (Table 6).

Table 6: Kinetic data of various models for release study of Acyclovir matrix tablets

Formulation code	Zero order		First order		Matrix		Peppas			Hixon Crowell		Best Fitted Model
	R	K	R	K	R	K	R	K	n	R	K	
F1	0.906	9.932	0.986	-0.107	0.968	23.093	0.998	15.455	0.245	0.989	-0.054	Peppas
F2	0.924	9.914	0.972	-0.069	0.952	17.125	0.997	14.564	0.236	0.982	-0.045	Peppas
F3	0.975	9.831	0.962	-0.058	0.951	11.897	0.996	12.125	0.219	0.994	-0.085	Peppas
F4	0.933	8.325	0.985	-0.099	0.932	12.865	0.986	8.256	0.224	0.983	-0.054	Peppas
F5	0.973	6.235	0.980	-0.022	0.963	9.456	0.983	11.546	0.264	0.978	-0.028	Peppas
F6	0.971	5.264	0.9590	-0.050	0.986	8.145	0.987	10.256	0.263	0.964	-0.034	Peppas
F7	0.934	7.456	0.9685	-0.052	0.978	18.154	0.991	9.124	0.249	0.974	-0.025	Peppas
F8	0.961	7.152	0.9535	-0.070	0.956	15.235	0.987	13.155	0.277	0.964	-0.098	Peppas

*R is drug release, k is rate constant for each model and n is the diffusion coefficient.

Swelling Index

The water uptake study or swelling index was performed for optimized formulation- F4 containing HPMC K100M. It showed that swelling is increased up to 50 % in six hrs. This may be due to high molecular weight and high viscosity. The results are shown in Table 7.

Accelerated stability studies

Accelerated stability studies were performed for optimized formulation F4 as per ICH guidelines for 1 month. The results did not reveal significant changes in color, hardness, percentage swelling index, drug content, percentage CDR by the end of 30 days at accelerated conditions of temperature and humidity. Thus, the formulation exhibited good stability and the values were within permissible limits. (Table 7).

Table 7: Accelerated stability studies carried out for optimized formulation F4 at 40±2°C/ 75±5% RH

Days	Colour	Hardness (kg/cm$^{2)}$	%Swelling index	%Drug content	% CDR
0	White	7.2	29.28	98.93	97.41
15	White	7.5	36.15	98.85	96.82
30	White	7.3	45.01	98.90	97.13

%CDR: Controlled drug release

CONCLUSION

Results of current investigation reasonably proved that hydrophilic polymer—HPMC K100 could be effectively employed for formulating control release matrix tablets of acyclovir. The promised F4 formulation was capable of controlling the medicament release up to 12 h and can overcome the hindrances associated with frequent administration of conventional acyclovir tablets.

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