Formulation and Evaluation of Gastro Retentive Mucoadhesive Sustained Release Pellets of Acyclovir

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A b s t r a c t

Acyclovir is an antiviral drug, belonging to the deoxyguanosine family, widely prescribed for the treatment of herpes simplex viral infections, as well as in the treatment of herpes zoster (shingles). Oral bioavailability of acyclovir is very low (10–20%) owing to its first pass metabolism with elimination half-life ($t_{1/2}$) of 2-3 h. It has absorption window in upper gastrointestinal tract. Due to its rapid elimination from site of absorption and short biological half life, sustained release formulation system for acyclovir is advantageous. In this study, gastro retentive mucoadhesive SR pellets of acyclovir was prepared using HPMC K 100M as matrix former and Sodium CMC as mucoadhesive polymer by extrusion spheronization technique. Acyclovir pellets prepared with higher concentration of HPMC (batch G) showed *in vitro* drug release for 12 h with sufficient mucoadhesion strength and ex vivo resident time. Release kinetic studies indicated that drug release data had best fit to Higuchi's model. In-vivo studies in rat model proved that relative bioavailability of acyclovir SR pellets get increased by 1.98 fold as compared plain drug suspension. The optimized formulation batch G was found to be stable during six months accelerated stability period.

Keywords: Acyclovir (ACV), Pellets, Mucoadhesion strength (MS), Ex vivo residence (ES), Dissolution

Introduction

For many decades, conventional dosage forms are used for the treatment of acute and chronic diseases which provide no control over the release of drug. To maintain the drug concentration within the therapeutically effective range, it is often necessary to administer the conventional dosage forms several times a day. This results in significant fluctuations in drug plasma levels and patient incompliance. Sustained release formulation has several advantages over conventional dosage formulation as it provides improved patient compliance and maintenance of steady state plasma drug concentration leading to better disease control and reduced intensity of local or systemic side effects.

Acyclovir or Acyclovir, chemically acycloguanosine, is a guanosine analogue antiviral is seen as the start of a new era in antiviral therapy, as it is extremely selective and low in cytotoxicity [1]. Mechanism of its antiviral activity involves selective conversion into acyclo-guanosine monophosphate (acyclo-GMP) by viral thymidine kinase, which is far more effective (3000 times) in phosphorylation than cellular thymidine kinase, subsequently the monophosphate form is further phosphorylated into the active triphosphate form, acyclo-guanosine triphosphate (acyclo-GTP), by cellular kinases. Acyclo-GTP is a very potent inhibitor of viral DNA polymerase. It has approximately 100 times greater affinity for viral than cellular polymerase. As a substrate, acyclo-GTP is incorporated into viral DNA, resulting in chain termination. The effective treatment of genital herpes simplex requires administration of 1000 mg of acyclovir in 5 divided doses a day. An alternative dose of 800 mg leads to plasma fluctuations; thus an SR dosage form of acyclovir is desirable [2, 3].

The aim of present study is to prolong the residence time of dosage form in stomach in order to improve the absorption of drug throughout upper gastrointestinal tract and subsequently bioavailability by formulating gastroretentive mucoadhesive SR pellets. Pellets dosage form was selected as it offers several advantages over single unit dosage forms [4-10]. In the pharmaceutical industry, pellets can be defined as agglomerates of fine powders or granules of bulk drugs and excipients [11].

Materials and Methods

Materials

Acyclovir was obtained as a gift sample from Cipla Pharamceutical Ltd. (India). HPMC K 100M (Methocel® K100M) obtained as gift sample from Colorcon Asia Pvt. Ltd. (India), Microcrystalline Cellulose (Avicel PH-102) and Sodium carboxy methyl cellulose

(Carmellose sodium) from Signet Chemical corporation (India). Other chemicals used were of analytical grade.

Saturation solubility study

Saturation solubility measurement was performed by standard shake flask method (BOEKEL, USA) at 37 ℃ at 20 rpm for 48 h. Solubility was determined in both water and 0.1N HCl (pH 1.2). For solubility study, an excess amount of the samples (20mg) were dispersed in 10 ml of media. After 48 h of shaking, samples were filtered through 0.2 µm membrane filters (PALL life sciences, India) and the filtrate was appropriately diluted with the medium used for solubility analysis. The measurement was conducted using UV-Visible Spectrophotometer V-530 at 254 nm (JASCO, Japan) [12].

Preparation of gastroretentive mucoadhesive SR pellets

Several batches have been prepared to achieve desire sustained drug release profile. MCC was used as an extrusion aid. Compositions for different batches are given in Table 1.

For pellets preparation all the ingredients were weighed accurately, mixed thoroughly and sifted through a 40 mesh sieve. This dry powder blend was transferred to Hobart mixer. The required amount of purified water (100 ml) was sprayed slowly to the powder blend and the system was mixed for 10 min with scraping the sides of the bowl and the blade at regular intervals. Wet mass obtained was fed into inlet of single screw extruder with 1 mm diameter (S.B. Panchal & company, India). The wet mass was extruded at speed of 45 rpm. The wet extrudate was spheronized for 10 min at 1000 rpm on a 12 cm diameter crosshatched plate of a spheronizer (Unisphere- lab spheronizer, S.B. Panchal & company, India). The pellets were dried in a hot air oven (Metalab, India) at 60 C for 6 h to achieve constant weight. Screening was carried out to separate oversized and undersized pellets. The pellets which were retained on 18 mesh sieve were collected. Sieving was carried out to get uniform sized pellets.

Coating of drug loaded pellets with mucoadhesive polymer

Pellets retained on 18 mesh sieve were used for coating purpose. Approximately 100g of ACV pellets subjected for coating in a 500 gm capacity lab scale coating pan. 1% solution of sodium carboxy methyl cellulose was prepared and sprayed over the pellet surface in tablet coater (Tablet pan coater MSW-709, Macro scientific works, India). Processing parameters involved, pan speed 32 rpm, spray rate 450mg/min, distance of gun from pellet bed was 12 cm and air pressure was kept at 1.5 kg/cm^2 .The polymer coating was done at level of 1% w/w and 3% w/w weight gain.

Characterization of drug loaded pellets

Particle size distribution

Particle size distribution was determined using mechanical sieve shaker. 10 g of the pellets were sifted through a series of sieves (12, 16, 18 and 24 mesh). The machine was operated for 5 minutes and % retained on respective sieve was calculated. The average particle size was determined.

Density and flow property

All formulation batches were also evaluated for their physical properties like bulk density, tap density (Veego, India), friability (Friability apparatus, Veego, India), flow property in terms of angle of repose [13]. All these parameters affect the processing of final formulation.

Loss on drying (LOD)

Loss on drying (LOD) was determined by gravimetric technique. A weighed quantity of pellets (10 g) were kept for drying in hot air oven at 60 C and loss in weight was calculated at regular time interval till constant weight.

Image analysis

The sphericity of the pellets was determined using derived pellet parameters measured by an image analysis system (optical microscope, DMWBI-223ASC motic digital microscope). A random sample of 150–200 pellets from each batch of product was examined and a roundness factor was calculated as follows:

Roundness factor = $P^2_m/4\ A$

Where, P_m is the perimeter length and A is the projected area. A perfectly round pellet would have a value of 1.0 irrespective of size and the value would tend towards 10.0 for pellets that were progressively non-spherical [14].

Swelling property

Swelling property was determined for each formulation batch. A weighed amount of pellets (10 g) were placed in a 100 ml measuring cylinder containing pH 1.2 media. Initial volume (V_o) was noted and change in physical volume was observed (V_t) at regular interval for 6 h [15]. The degree of swelling was calculated using following formula:

Degree of Swelling = V_t -V_o/V_o

Measurement of mucoadhesion strength

Mucoadhesive strength of the SR pellets was measured using reported modified physical balance method [16]. To make measurement easier, a disc of pellets were prepared using 10 mm standard flat surface punches on a single punch tablet machine (Cadmach, Ahmedabad, India)). A modified double beam physical balance was used in which the right pan has been replaced by a glass slide with copper wire and to make the right side weight equal with left side pan some additional weight was placed

(reference). The porcine gastric mucus membrane collected from local slaughter house was used as model membrane and a pH 1.2 solution was used as the moistening fluid. The porcine stomach mucosa was maintained in Tyrode solution at 37 C till further use. From the mucoadhesive strength, the force of adhesion was calculated using the following formula:

$$\text{Force of adhesion (N)} = \frac{\text{Bioadhesive strength} \times 9.81}{100}$$

$$\text{Bond strength (N/m}^2) = \frac{\text{Force of adhesion (N)}}{\text{Surface area of tablet (m}^2)}$$

Ex vivo residence time

The mucoadhesion property of SR pellets was determined according to earlier reported method [17]. A 5 cm long piece of freshly cut sheep intestine was obtained from a local slaughterhouse, cleaned by washing with isotonic saline solution and used within 1 hr of slaughter. An accurately weighed amount of pellet was placed on the mucosal surface, which was attached to a polyethylene plate that was fixed at an angle of 40° relative to the horizontal plane. pH 1.2 buffer maintained at $37\pm1℃$ was passed at a rate of 5 ml/min over the tissue. The time required for detaching all the pellets from mucosal surface of the sheep intestine was recorded by visual inspection. The experiments were performed in triplicate.

Determination of drug content

A weighed amount of SR pellets (10 mg) were ground to powder and suspended in 100 ml of purified water, shaken for 10 min and filtered. Filtrate was suitably diluted with purified water and analyzed using UV spectrophotometer V-530 a t 254 nm (JASCO, Japan) [18].

In vitro drug release

Dissolution test was carried out using six station USP XXIII (TDT-06T Electrolab, Mumbai, India) dissolution apparatus. Pellets equivalent to 50 mg of drug filled in capsule and subjected for dissolution. The test was performed at a paddle speed of 50 rpm in 900 ml of 0.1N HCl (pH 1.2) buffer for 12 h, temperature maintained at 37 ± 0.5 C. An aliquot of 5 ml was withdrawn and same amount of fresh medium was replaced to maintain the sink condition. The absorbance was measured after appropriate dilution at 254 nm using UV spectrophotometer. Drug concentration was determined using standard plot of absorbance versus drug concentration. Dissolution was performed in triplicate.

Mathematical model fitting of in vitro drug release

To analyze the in vitro release mechanism, data obtained from dissolution fitted to different kinetic models like zero order, first order, Higuchi and Korsmeyer Peppas [14, 19].

In vivo study

Animal experimental procedure

All experimental procedures were reviewed and approved by the institutional animal ethics committee of University department of chemical technology (Aurangabad, India). Wister rats were fasted for 24 h before the experiment and food was reoffered after 4h post-dosing. The rats were divided into two groups of five animals each. Each group was orally administered optimized batch G and plain Acyclovir suspension, equivalent dose of 40 mg/kg/ml of saline body weight as acyclovir. Blood samples were collected from retro-orbital venous plexus of rats at predetermined time intervals (t = 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 h). Blood sample was centrifuged for 10 min to separate plasma at 4000 rpm (research centrifuge TC 4100 D, Remi, India) and stored at -20 C till further analysis.

Extraction procedure and analytical conditions for Acyclovir

100 µl rat plasma samples was taken in centrifuge tube and mixed well. Then 100 µl 12 .5% trichloroacetic acid solution was added and vortex for 1 minute. The mixture was centrifuged at 9000 rpm for 10 min, and 150 µl of the resultant supernatant was transferred to a clean centrifuging tube and neutralized with 50 µl 1M NaOH. To remove substances that interfere with the objective peaks in the chromatograms, 500 µl n-hexane was then added. The mixture was vortex for 1 minute and centrifuged at 9000 rpm for 10 min. After aspirating the organic layer, 50 µl of the resultant aqueous layer was injected onto the HPLC system (19). The liquid chromatograph (Jasco LC-10AS, Kyoto, Japan) was equipped with column (150mm×4.6mm, 5µm) attached to a C18 guard column (7.5mm×4.6mm, 5µm) at 40 C. The mobile phase consisted of methanol and water in ratio of (1:99) adjusted to pH 2.0 with perchloric acid. Flow rate was kept 1 ml/min, and detection was carried out using a UV detector (Shimadzu SPD-10A) at 280 nm. The method was linear between 5 and 25 µg/ml.

Stability study

Optimized formulation (batch G) was subjected for stability study. Stability study was carried out as per ICH guidelines [21]. The prepared pellets were stored in a humidity chamber with relative humidity of 75 ± 5 % and temperature of 40 ± 2 ℃ or at room temperature for 6 months. Samples were withdrawn at time 0, 1, 3 and 6 months. Samples were evaluated for their physical characteristics, dissolution behavior and drug content.

Fourier transform infrared spectroscopy

Drug polymer interaction was studied by FTIR spectroscopy (OPUS, Bruker, Germany). The spectra were recorded for pure drug and drug loaded pellets using FTIR. Samples were prepared as potassium bromide (KBr) disks by means of a hydrostatic press.

The scanning range was 550 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

Differential scanning calorimetry

DSC analysis was performed using PERKINELMER DSC Pyris -6 (USA) on 2 to 8 mg sample. Sample was heated in an aluminum pan at a rate of 10 ℃ / min within a 30 to 300℃ temperature range under a nitrogen flow of 20 ml/min. An empty sealed pan was used as a reference.

Results and Discussion

Saturation solubility

Solubility of acyclovir was found to be 2.4 mg/ml and 0.66 mg/ml in water and pH 1.2 buffer respectively. Drug content analysis of all the formulation batches showed high drug content uniformity with 98.5-100.5% ACV.

Particle shape and size distribution

Image analysis indicated that pellets from C, F and G batches produces spherical particles with roundness factor 0.999, 1 and 1 respectively. Batches A and E had rod shaped irregular pellets whereas batches B, D and H produced variable sized pellets Figure 1. Roundness factor for all the batches are provided in table 2. Sieve analysis showed that 96-99% of pellets fall under particle size of 1000 μm and showed uniform particle size distribution (Table 3).

Table 2. Pellets shape defining roundness factor

Batch No.	Roundness factor
A	1.514
B	1.000
C	0.999
D	1.197
E	1.411
F	1.000
G	1.000
H	0.999

Density

Bulk density and tap density are the measures for bulkiness of a formulation. Result showed that there were no significant differences observed in bulk density and tap density due to spherical shape of pellets.Values obtained from angle of repose indicated that prepared pellets had good flow. Pellets friability was found to be within pharmacopoeial acceptable range and there was no significant loss in weight observed on drying. Data for physical parameters evaluation given in table 4.

Degree of swelling

From A to D, maximum swelling was found at 4 h; from these, D was found to show high swelling of 500.85° at 4 h. Degree of swelling for E and H was also found to be nearly same as D whereas maximum swelling property was observed with F and G Batch at 3 h. The comparison of degree of swelling of all formulations is shown in Figure 2. It was observed that as the HPMC K 100M concentration in formulations increases, swelling property gradually increases Figure 2.

Mucoadhesion strength and Ex vivo residence time

All the formulations batches were evaluated for these parameters in triplicate (Table 5). Gradual increase in mucoadhesion strength (MS) and ex vivo residence (ER) time was observed from batch A to H. This adhesive property will increase with the degree of hydration until a point where over hydration leads to a sudden decline in MS, which might be due to the disentanglement at the polymer/tissue interface. The degree of swelling was increased with the increase in the concentration of Na CMC and HPMC K 100M . Batch A was found to have low MS and ER of 3.33 g and 2.43 h, respectively. MS and ER for different batches are given in Table V. For uniform and prolonged release of drug, an appropriate degree of swelling and mucoadhesion is required. The maximum MS and ER was found for batches G and H.

Table 5. Results of mucoadhesion strength and ex vivo residence time of all pellets formulations

Batch no.	MS (g)	ER (h)
A	3.33±0.031	2.43±0.231
B	4.15±0.022	3.74±0.312
C	6.42±0.021	5.5±0.271
D	8.25±0.023	7.56±0.312
E	10.27±0.020	6.85±0.501
F	13.5±0.023	8.34±0.541
G	16.34±0.031	7.01±0.461
H	18.45±0.023	9.56±0.801

In vitro drug release

The comparison of cumulative drug release of all formulations is shown in Figure 3 and Figure 4 as well as in table 6. Formulations A, B and C were found to release approximate 40% of drug within first hour whereas formulation D released 25% drug in the same time but these formulations were able to sustain the release upto 8 h only. An ideal sustained release system should be able to release the drug immediately to attain the therapeutic level at a faster rate and maintain this drug level for a prolonged period of time. Formulation batches from E to H showed 25% drug release within first hour and able to sustain the drug release for 12 h due to the presence of higher amount of HPMC K 100M and Na CMC coating level. The drug release profile of formulations F and G was found to be same. Formulation G was taken as an optimized batch

since it had higher MS, ER and desired drug release profile. The optimized formulation G showed good drug content uniformity and insignificant change in dissolution profile during the stability period.

The n and R^2 values for zero order, first-order, Higuchi and Peppas were represented in Table 7.The results indicated that the best linearity was found in Higuchi's equation (r^2 = 0.9948) indicating the release of drug from matrix as a square root of time dependent process based on Fickian diffusion. The value of the release exponent (n) in acyclovir sustained release obtained as 0.2135 (was very low) which is beyond the limit value of 0.5-1 of Korsmeyer model so-called power law. So as per n value drug release mechanism was found to be very complex involving swelling, diffusion and erosion. Generally water penetration, polymer swelling, drug dissolution, drug diffusion and matrix diffusion from dosage form are controlled by rate of hydration of HPMC, which forms a gel barrier [16].

Pharmacokinetic study

The mean plasma concentration of ACV-time profiles after oral administration of acyclovir loaded mucoadhesive pellets and acyclovir suspension are illustrated in Figure 5. After administration of the drug suspensions, plasma drug concentration achieved at its maximum level within 1 hand then decreased rapidly whereas the profiles for drug-loaded mucoadhesive pellets (batch G) was found to be constant. A peak plasma concentration was observed in 2 h, which could be kept in a relatively steady state for 8 h and plasma concentration falls below detection level in 12 h. The pharmacokinetic parameters are listed in Table 8. The Cmax values for acyclovir loaded gastroretentive mucoadhesive pellets and acyclovir suspension were 598 ng/ml and 674 ng/ml, respectively. The oral bioavailability of acyclovir was greatly improved as the relative bioavailability values was 198% for acyclovir loaded mucoadhesive gastroretentive pellets compared with that of acyclovir suspension, which was attributed to the prolonged residence of microspheres in gastrointestinal tract and induced close contact of drug at its absorption site to enhance the absorption

Fourier transform infrared spectroscopy

Acyclovir has characteristic band in IR, NH stretching: a single band at 3552 cm^{-1}, NH stretching: a forked band at 3500 cm^{-1}, OH stretching: a broad peak at 3315 cm^{-1}, -CH stretching (aromatic) a single band at 3184 cm^{-1}, –CH stretching (aliphatic) a single band at 2712 cm^{-1} (This was normally observed at 2933 cm^{-1}, however due to the intramolecular hydrogen bond between the –NH$_2$ and –OH, it was shifted to 2712 cm^{-1}), HC (=O)NH$_2$ stretching (Cyclic amide): a single peak at1716 cm^{-1}.The FTIR spectral analysis showed that there was no appearance or disappearance of any characteristic peaks of acyclovir in the optimized formulation, confirms the absence of chemical interaction between drug and polymers Figure 6.

Differential scanning calorimetry

DSC thermograms of ACV and optimized SR pellets formulation containing ACV and polymer were shown in Figure 7. A sharp endothermic peak (Tm) at 252.22 ℃, with the enthalpy of fusion being 455.399 J/g, corresponding to melting point of ACV was obtained. DSC thermogram of optimized formulation did not show any change in ACV sharp endothermic peak indicated absence of chemical interaction between drug and polymer and suitability of formulation.

Table 1. Formulation compositions of different SR pellets batches

Sr. no.	Ingredients (g)/Batch Code	A	B	C	D	D	E	F	H
1	Acyclovir	20	20	20	20	20	20	20	20
2	HPMC K 100 M	10	10	20	20	30	30	40	40
3	Microcrystalline cellulose	70	70	60	60	50	50	40	40
4	Sodium CMC	1%	3%	1%	3%	1%	3%	1%	3%
5	Magnesium stearate	1%	1%	1%	1%	1%	1%	1%	1%

Table 3. Particle size distribution (n=3, ±SD)

Batch No.	% of pellets retained on screen mesh*			
	1700 µm	1180 µm	1000 µm	710 µm
A	0.0000±0.000	0.0666±0.066	99.1333±0.570	0.8000±0.600
B	0.2000±0.115	1.8000±1.102	97.2666±1.636	0.4000±1.302
C	0.0666±0.066	1.3333±0.941	97.8666±1.334	0.7333±0.467
D	0.1333±0.066	2.0000±1.502	96.8666±2.436	1.0000±1.001
E	0.3333±0.333	1.2666±1.074	96.7333±2.387	1.6666±1.472
F	0.1333±0.133	0.7333±0.732	98.333±1.169	0.8000±0.305
G	0.6667±0.176	0.9333±0.353	98.2000±0.503	0.1333±0.133
H	0.6000±0.305	0.4666±0.176	98.4666±0.266	0.4666±0.134

Table 4. Physical characterizations of SR pellets (n=3, ±SD)

Batch	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose ( )	Friability (%)	Loss on drying (%)
A	0.7702 ± 0.028	0.7896 ± 0.002	18	0.2	0.2
B	0.7563 ± 0.032	0.8700 ± 0.013	22	0.4	0.0
C	0.7780 ± 0.026	0.8183 ± 0.014	25	0.2	0.1
D	0.7408 ± 0.015	0.8256 ± 0.028	24	0.2	0.0
E	0.7473 ± 0.009	0.8026 ± 0.000	19	0.2	0.0
F	0.7400 ± 0.002	0.7913 ± 0.003	18	0.4	0.3
G	0.8220 ± 0.003	0.8430 ± 0.023	20	0.4	0.0
H	0.7306 ± 0.009	0.8326 ± 0.014	18	0.0	0.0

Table 6. *In vitro* drug release of all acyclovir SR pellets batches (n=3, ±SD)

Time (h)	Percent Cumulative Release							
	Batch A	Batch B	Batch C	Batch D	Batch E	Batch F	Batch G	Batch H
0	0	0	0	0	0	0	0	0
1	40±2.1	35±2.27	34±3.1	30±2.2	28.01±2	29.73±2.1	27.78±3	18.45±2.2
2	50±4.3	40.62±3.4	45.64±3.3	32±3.3	40.3±4.3	41.43±3.0	40.18±3.5	32.58±3.3
3	60±4.1	51.16±4.5	56.16±3.5	45.5±5	47.27±4	51.09±4.3	46.54±3.5	42.58±3.8
4	65.6±3.	62.95±3.3	66.38±4.1	60.32±3	53.26±3	60.28±3.5	58.12±4.0	50.12±3.4
5	75.4±4	75.98±4.4	74.41±3.5	75.14±4	59.45±4	69.35±4.2	62.12±3.4	57.12±4.3
6	85.5±3.5	86.21±3.1	85.96±3.6	84.96±3	65.86±3	76.89±3.4	75.12±3.5	63.18±3.5
7	95±3.4	93.45±5	95.48±4.5	94.15±4	72.78±3	83.43±5	79.25±4.3	66.96±3.2
8	99±3.2	100.21±4	101.05±3	99.25±3	79.07±2	86.68±4.1	82.18±3.3	70.78±3
9	-	-	-	-	85.23±4	89.77±3.2	85.36±2.1	75.65±4
10	-	-	-	-	90.75±4	93.22±4.8	88.89±3.9	78.69±3.3
11	-	-	-	-	95.79±3	96.17±3	95.12±4.4	89.24±3.3
12	-	-	-	-	99.84±4	98.25±2	99.45±3.2	94.17±4

Table 7. Kinetics of *in vitro* drug release of all formulations

Batch No.	Zero order R^2	First order R^2	Higuchi R^2	Korsmayer- Peppas	
				R^2	n
A	0.9926	0.9037	0.9251	0.9892	0.4216
B	0.9158	0.9392	0.9839	0.9901	0.2984
C	0.9518	0.9025	0.9930	0.9838	0.2778
D	0.9829	0.8274	0.9422	0.9538	0.4360
E	0.9428	0.6980	0.9935	0.9846	0.2141
F	0.8901	0.9600	0.9926	0.9429	0.2043
G	0.9153	0.8022	0.9948	0.9565	0.2134
H	0.9430	0.9130	0.9904	0.9313	0.2512

Table 8. In-vivo pharmacokinetic parameters and relative bioavailability of formulation G SR pellets and ACV suspension.

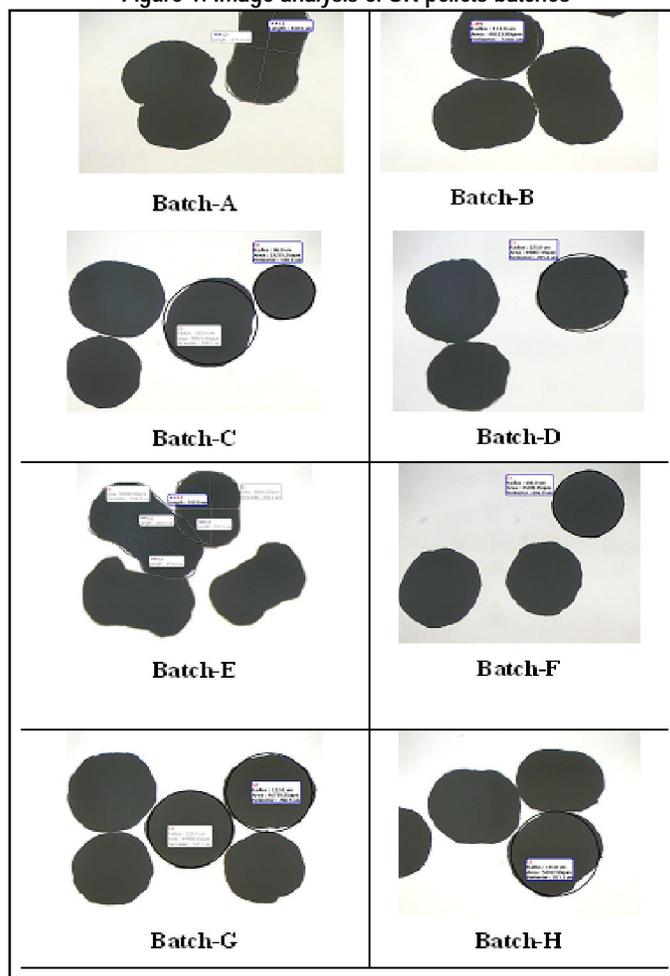| Formulation	Tmax (h)	Cmax (ng/ml)	AUC $_{0-12h}$ (ng.h/ml)	Fr (%)
ACV suspension	1.10± 0.25	598±0.54	3231.23±214.54	100.00
ACV SR pellets (G)	1.15±0.34	674±0.87	6397.38±324.65	198.00
n = 6; Data are means ±SD				

Figure 1. Image analysis of SR pellets batches

Batch-A

Batch-B

Batch-C

Batch-D

Batch-E

Batch-F

Batch-G

Batch-H

Figure 2. Degree of swelling vs time profile of all SR pellets formulation
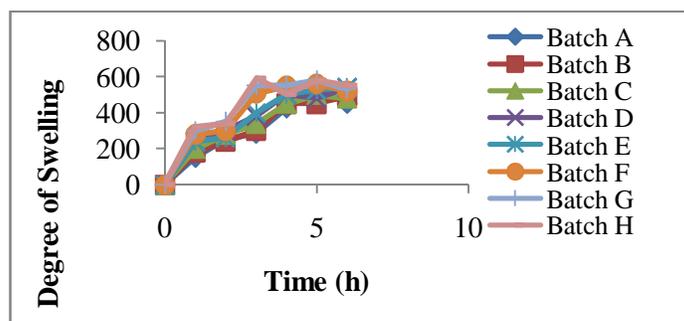
Figure 3. *In vitro* drug release of acyclovir SR pellets
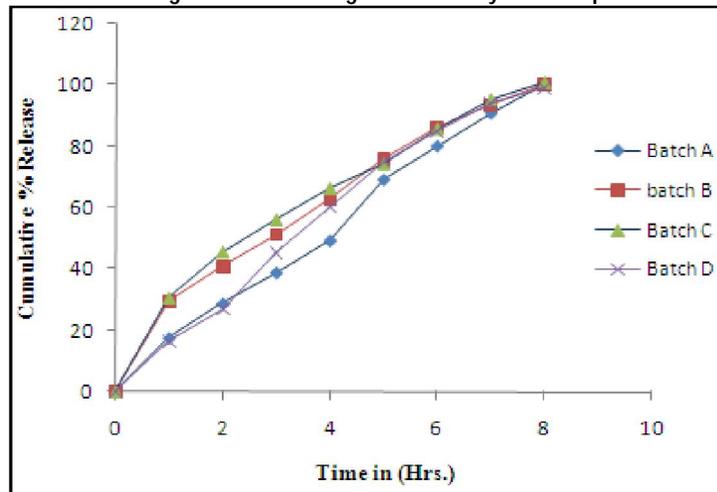
Fig 4. *In vitro* drug release of acyclovir SR pellets.
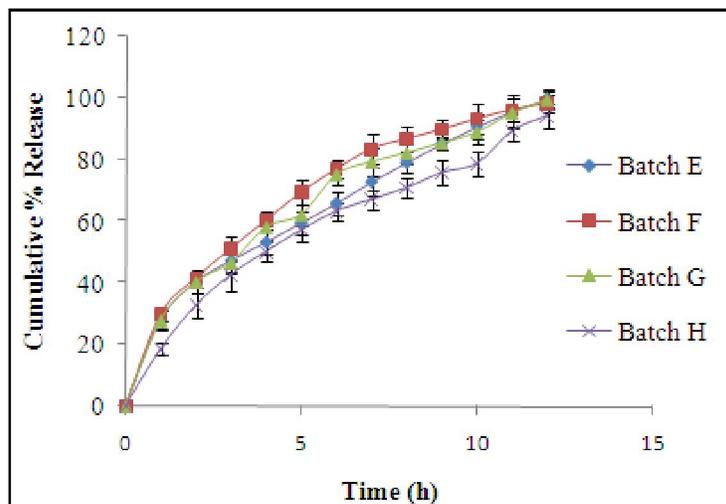
Figure 5. Plasma concentration time profiles of ACV suspension and formulation G SR pellets
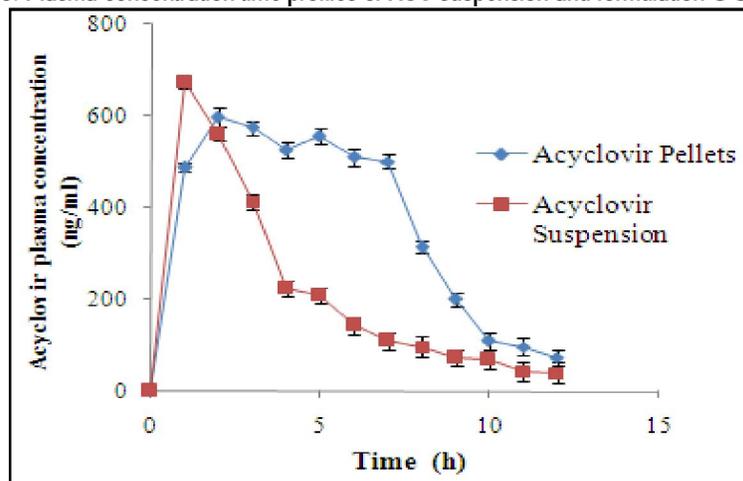
Figure 6. FTIR spectra of (A) ACV, (B) microcrystalline cellulose, (C) Sodium CMC, (D)HPMC K 100M and (E) Optimized formulation
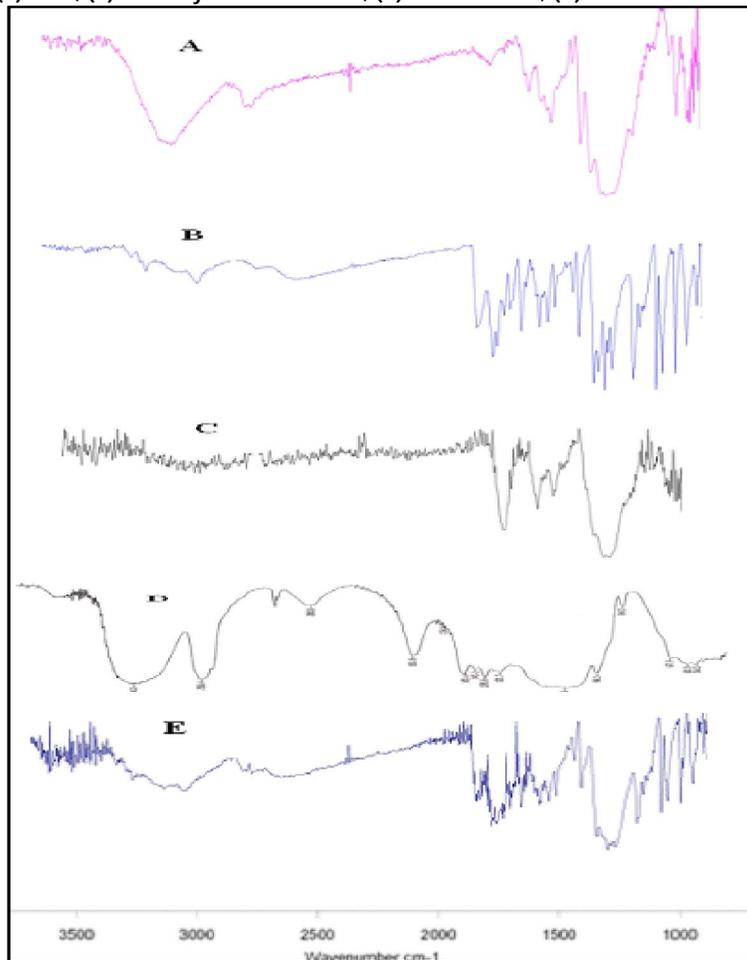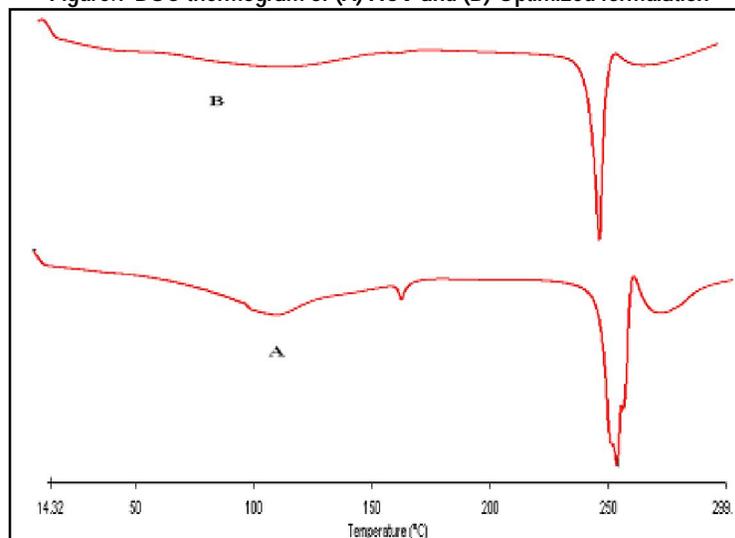

Figure.7 DSC thermogram of (A) ACV and (B) Optimized formulation

Conclusions

Sustained release pellets of acyclovir was developed using HPMC K 100M matrix forming agent by the extrusion spheronization method showed good results in terms of mucoadhesion, ex vivo residence time, sustained drug release. Kinetic models revealed that it follows Higuchi's model and drug release by complex mechanisms of swelling, diffusion and erosion. Relative bioavailability of SR pellets also gets increased by two fold. Optimized formulation was found to be stable for the period of stability study. In conclusion, we suggest that SR system for acyclovir administration can be alternative way to conventional system as it offers several advantages such as increased bioavailability, sustained drug release and improved patient compliance.

Author's contribution

Mr. Sandip Gite, the main author, has performed the literature survey and designed the whole work, Mr. Ajay Sav has helped

during animal study and HPLC method development. Mr. Vishal Morade contributed in manuscript drafting. Dr. Sachin Bhusari who has supervised our work at each and every process step and made all process smooth by providing his intellectual knowledge and permission to use departmental facility for experiment.

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