British Journal of Pharmaceutical Research
7(6): 428-439, 2015, Article no.BJPR.2015.123
ISSN: 2231-2919

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Formulation and Evaluation of Sustained Release Gastro-retentive Drug Delivery System of Acyclovir Leading to Enhanced Bioavailability

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Authors' contributions

This work was carried out in collaboration between both the authors. Author SK designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author SKM managed the literature searches, analyses of the study performed the spectroscopy analysis and both the authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJPR/2015/19116
Editor(s):
(1) Nighat Sultana, Pakistan Council of Scientific and Industrial Research Laboratories Complex, Pakistan.
Reviewers:
(1) Anonymous, Wits University, South Africa.
(2) Sachinkumar Vasantrao Patil, Department of Pharmaceutics, Ashokrao Mane College of Pharmacy, Maharashtra, India.
Complete Peer review History: http://sciencedomain.org/review-history/10208

Original Research Article

Received 26th May 2015
Accepted 18th June 2015
Published 16th July 2015

ABSTRACT

Objective: The objective was formulation and characterization of low-density gastro-retentive microspheres of Acyclovir (ACV) using hydroxyl propyl methyl cellulose to enhanced retention time and bioavailability.
Materials and Methods: HPMCK4M was used as polymer for forming microspheres and Poly Vinyl Alcohol as stabilizing agent. The microspheres were characterized with respect to their morphology, particle size, encapsulation efficiency, production yield, in-vitro release and pharmacokinetic study in rats. The mean particle size was within range and showed spherical shape.
Results and Discussion: Microspheres were having sufficient entrapment efficiency and floating ability and were directly proportional to the polymer concentration. In-vitro and pharmacokinetic study in rats proved the efficiency of microspheres in sustaining the drug release for 12 hrs as

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compared to oral suspension of ACV.
Conclusion: The floating microspheres of ACV are potential drug delivery system for the enhancement of oral bioavailability of ACV.

Keywords: Acyclovir; microspheres; emulsion solvent evaporation; encapsulation efficiency; floatation.

1. INTRODUCTION

Acyclovir [9-(2-hydroxyethoxymethyl) guanine] (ACV), a synthetic purine nucleoside analog derived from guanine, is one of the most effective antiviral drug. ACV is the first drug to be licensed and most widely used for the treatment of *Herpes simplex* virus HSV-1, HSV-2 and Varicella Zoster (VZV) virus [1]. It interferes with DNA synthesis and inhibits viral replication. ACV is currently marketed as capsule (200 mg) and tablet (200 mg) and topical ointment. Unfortunately, the absolute oral bioavailability of ACV is considerably poor (about 15–30%) because of its low water-solubility (about 0.2%, 25°C) and short half-life (about 2.5 h) [2]. The absorption of ACV is highly variable and dose dependent. It is soluble in acidic pH and is predominantly absorbed from the upper gastro intestinal tract (GIT) by active transport, once this dosage form passes the absorption window; the drug will be neither bioavailable nor effective [3]. Brief gastric emptying time in human ranging between 2-3 hr through the major absorption zone results in incomplete drug release and excretion of major part of the administered dose in unabsorbed form resulting in low bioavailability and efficacy [4]. The phenomenon of absorption via a limited part of the GIT has been termed the narrow absorption window. Therefore ACV must be taken in an oral dose of 200 mg five times daily, which cause compliance problems to patients. To overcome the oral absorption barrier, controlled release delivery systems containing ACV have been developed to improve its bioavailability. These are however associated with physiological difficulties of inability to retain and locate the controlled drug delivery system within the desired region of GIT, due to variable gastric emptying and motility [5]. So, it can be envisaged that increasing the residence time in the upper GIT can enhance absorption and subsequently the bioavailability of ACV [6]. Floating drug delivery systems retains the dosage form at the site of absorption and thus enhances the bioavailability. It is low-density system, which is having a sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period [7]. While the system floats over the gastric content, the drug is released slowly at the desired rate. It results in increased gastro-retentive time and reduces fluctuation in the plasma drug concentration. Single unit floating devices are associated with unreliability and non-reproducible in prolonging residence time due to “all or none effect” and can also lead to local irritation due to large amount of drug delivered at specific site. In contrast multiple unit particulate dosage forms have the advantage of uniform pass-out through the GIT and reducing the inter-subject variability and chances of local irritation [8].

So it was aimed to develop floating microspheres of ACV which is capable of floating on gastric fluid and delivering the therapeutic agent over an extended period of time leading to improved oral bioavailability. The physicochemical characteristics, in vitro/in vivo buoyancy properties and pharmacokinetics in rats were investigated.

2. MATERIALS AND METHODS

Acyclovir, Hydroxyl Propyl Methyl Cellulose (4000 mPas) was kindly provided by Ranbaxy research lab, Gurgaon, India. Dichloromethane and Polyvinyl alcohol (low viscosity grade) were procured from S.D Fine Chemicals Ltd. All other reagents were of analytical grade.

2.1 Preparation of Microspheres

Floating microspheres were prepared by emulsification solvent evaporation method by varying the concentration of polymer (HPMC K4M) keeping the stabilizer concentration constant and further varying the concentration of stabilizer (PVA) on keeping all other factors constant as detailed in Table 1. The dispersed phase was constituted by dissolving Hydroxypropyl methylcellulose (HPMC K4M) in dichloromethane. ACV was further added to it with continuous stirring on magnetic stirrer. PVA at different concentration was added in distilled water (100 ml) and allowed to cool to 9-12°C prior to use as continuous phase. The dispersed phase was added with the help of syringe to the continuous phase under continuous stirring. The emulsion obtained was stirred for 5 to 6 h at

40°C to allow solvent evaporation using mechanical stirrer at 2500 rpm mounted on a stirrer plate with temperature control. The microspheres were recovered by centrifugation and subsequent filtration through 0.22 µm membrane filter. The microspheres were rinsed with cool distilled water 3 times and dried at 40°C overnight under vacuum. The formulations were made in triplicate.

2.2 Characterization of Floating Microspheres

2.2.1 Particle size analysis

The particle size distribution in terms of average diameter of the microspheres was determined using a stage micrometer scale. Dry microspheres were suspended in distilled water and ultrasonicated for 5 sec. A drop of suspension was placed on a clean glass slide and at least 100 particles were counted under stage ocular micrometer. The study was conducted in triplicate.

2.2.2 Shape and surface morphology of microspheres

The shape and surface characteristics of microparticles were followed by scanning electron microscope (JSM 5610 LV SEM, JEOL, Datum Ltd., Japan). Samples of pellets were dusted onto a double-sided tape on an aluminum stub. Afterwards, the stub containing the sample was coated with gold using cool sputter coater (Polaran E 5100) to a thickness of 400 A°. SEM images were taken at the accelerated voltage of 15 KV and chamber pressure of 0.6 mm Hg.

2.2.3 Percentage yield

The prepared microspheres were collected and weighed. The yield was calculated by dividing the measured weight by the total weight of all non-volatile components. The percentage yield of microspheres was calculated as follows for (n=3).

% yield =

[(Theoretical weight of drug and polymer)/ (Weight of microspheres)] x 100 (1)

2.2.4 Determination of drug entrapment efficiency

The microspheres equivalent to the ACV 30 mg were accurately weighed and dissolved in 10 ml of 0.1 N HCl. The solution was stirred by magnetic stirrer for 4 hrs. Next 1 ml of solution was transferred to 50 ml volumetric flask and diluted with 0.1 N HCl to the volume. The solution was then filtered through whatman filter paper no. 44. The amount of ACV was assayed at 254 nm using 0.1 N HCl as blank by UV spectrophotometer 1700 Pharmaspec, Shimadzu, Kyoto, Japan.

The entrapment efficiency was calculated from the ratio of actual amount of drug determined to that added initially in the solution.

% Drug entrapment =

[(Calculated drug content)/ (Theoretical drug content)] x 100 (2)

2.2.5 Floating lag time

The microspheres were placed in 100ml beaker containing 0.1 ml HCl. The time required for raising the surface and float was determined as floating lag time.

Table 1. Formulation optimization of floating acyclovir microspheres (n=3)

Code	Drug: polymer	HPMCK4M (mg)	Dichloromethane (ml)	Polyvinyl alcohol (%w/v)	Water
MA1	1:1	100	10	0.2	q.s
MA2	1:1.5	150	10	0.2	q.s
MA3	1:2	200	10	0.2	q.s
MA4	1:3	300	10	0.2	q.s
MA5	1:3	300	10	0.3	q.s
MA6	1:3	300	10	0.4	q.s
MA7	1:3	300	10	0.6	q.s
MA8	1:3	300	10	0.8	q.s

2.2.6 Floating ability of microspheres

Accurately weighed quantity (100 mg) of microspheres were placed in 0.1 N HCl in 100 ml volumetric flask containing 0.02% Tween 20 and stirred at 100 rpm. After agitation for a predetermined time interval, the microspheres that floated over the surface of the medium and those settled at the bottom of the flask were recovered separately. The microspheres were dried in the desiccator and were weighed and their buoyancy was calculated using the following equation

% Buoyancy =

[(Weight of microspheres floating on the surface)/ (Weight of floating + non-floating microspheres)] x 100 (3)

2.2.7 *In-vitro* dissolution studies

The in-vitro release of ACV from microspheres was performed in 900 ml of simulated gastric fluid (pH 1.5) containing 0.5% Tween 80, which was based on USP XXII method (Dissolution apparatus at 50 rpm and 37 ± 0.5°C). Microsphere formulation (Single dose containing 200 mg of ACV) was placed in the apparatus and 1ml sample was withdrawn at predetermined time intervals and was immediately replaced with fresh amount of simulated gastric fluid. The aliquots of 1ml were withdrawn and diluted with 5 ml of simulated gastric fluid containing 0.5% Tween 80 and analyzed for the drug content by using UV-spectrophotometer at 254 nm. [22]

2.2.8 Micromeritic properties of microspheres

The optimized formulation was characterized for their micromeritic properties, such as bulk density, tapped density, Hausner's ratio, Carr's compressibility index and flow property.

2.2.9 Determination of bulk density and tapped density

1 gm of floating microspheres of optimized formulation was subjected into 10 ml graduated measuring cylinder separately and the volume was noted down. The bulk density and tapped density was determined by using following formula.

Bulk density =

[(Weight of the fixed mass of microspheres)/ (Bulk volume of the microspheres)] (4)

Tapped density =

[(Weight of the fixed mass of microspheres)/ (Tapped volume of the microspheres)] (5)

2.2.10 Determination of hausner's ratio and carr's compressibility index

The density determinations were used to determine the Hausner's ratio and could be determined using following formula.

Hausner's ratio =

[(Tapped density)/ (Bulk density)] (6)

Carr's compressibility index =

[(Tapped density - bulk density)/ (Bulk density)] x 100 (7)

2.2.11 Angle of repose (θ)

Angle of repose (θ) of the microspheres was determined by a fixed height funnel method, which measures the resistance to particle flow. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. An accurately weighed sample of the microspheres was allowed to pass through the funnel freely on to a flat surface. The height (h) and radius (r) of the powder cone were measured and the angle of repose Ø can be calculated as

$$Ø = \tan^{-1} h/r \quad (8)$$

2.2.12 X-ray diffraction studies

X-ray diffractograms of ACV, placebo microspheres and optimized formulation was recorded using D8 Advance X-ray diffractometer (Bruker AXS D8 Advance®, Germany). The sample was irradiated with Nickel filtered 2.2 KW CuAnode, Dermic X-ray tube, equipped with a sample holder, with zero background and PMMA & Lynux eye detector. The samples were scanned between 0-70° at 2θ scale.

2.3 Comparison of Optimized Formulation with Marketed Formulation

One formulation of ACV immediate release (IR) available in the Indian market was checked for drug release profile (200 mg, Zovirox, Cipla Ltd.). The release rate of ACV from the capsules was

determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1N HCl, at 37 ± 0.5°C and 50 rpm. 1 ml sample solution was withdrawn from the dissolution apparatus for 1 h, and there after every 1 h upto 4 h. Samples were replaced by its equivalent volume of dissolution medium. The samples were filtered through Whatman filter paper and solutions after appropriate dilution were analyzed at 254 nm by UV Spectrophotometer.

2.4 Pharmacokinetic Study of Acyclovir Microspheres

Rats (Sprague Dawley), 6 to 8 months old, weighing 200–220 g were divided into three groups, each consisting of six animals. The protocols for these investigations were approved by the Institutional Animal ethics committee in accordance with the disciplinary principles and guidelines of CPCSEA (registration no 723/02/a/CPCSEA). Rats were kept on fasting 12 h before drug administration and until 24 h post dosing. Water ad libitum was given throughout the study. The first group received an oral administration of 0.1 % sodium CMC suspension (normal control). The second group received an oral administration of 4 % drug solution in sodium CMC suspension. A 240 mg sample of microsphere (MA7) corresponding to 40.0 mg of ACV was suspended in 2.0 ml saline and administered orally using a feeder tube under non-anesthetic condition to the third group. At 1, 2, 4, 8, 12 and 24 h time intervals, blood samples were collected from jugular vein in ependorff tubes and centrifuged at 3000 rpm for 10 min (REMI Equipment, Mumbai, India). Supernatant liquid was collected, filtered through a 0.45 µm filter into volumetric flask and the drug concentration was determined by using LC/MS/MS.

3. RESULTS AND DISCUSSION

3.1 Particle Size Analysis

The micro particles were formulated with varying concentration of polymers to access the effect of polymer on particle size. The particle size of the microspheres (MA1-MA4) was in range of 225.3±5.67 to 390.5±5.36 µm (Table 2). The mean particle size of the microspheres increased significantly with increase in the concentration of polymer. The viscosity of the medium increases at a higher polymer concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities resulting in the formation of larger droplets consequently larger microspheres [9]. It can also be demonstrated that the concentration of PVA (stabilizer) has marked effect on the particle size of the microparticles. The particle size decreased from 390.5±7.79 to 369.4±5.36 µm with increase in PVA concentration (MA5 to MA8) as it allows the emulsion to stabilize to a greater interfacial area and preventing coalescence [10].

3.2 Shape and Surface Morphology of Microspheres

The SEM images revealed the crystalline nature of the pure ACV as shown in Fig. 1(a). The shape of the microspheres was spherical and hollow in nature. The outer surface of the microsphere was little irregular which gets smooth on increasing the concentration of PVA. The SEM images signify the uniform distribution of the drugs in the walls of the

Table 2. Characterization of the different formulation of acyclovir microspheres (MA1 –MA8) (n=3)

Code	Particle size	Percentage yield	Percentage entrapment efficiency (% ± SD)	Floating ability (%)	% CDR
MA1	225.3±5.67	62±1.71	52.18±3.84	72.21±1.48	89.41±0.89
MA2	232.8±7.32	67.5±2.64	55.32±2.75	75.34±1.75	86.81±1.32
MA3	245.20±4.78	69.28±1.93	59.73±2.75	79.23±0.97	85.17±2.79
MA4	325.8±6.87	72.37±2.37	61.01±3.22	81.18±1.21	83.13±0.87
MA5	390.5±7.79	79.51±3.04	64.95±2.84	83.97±2.37	85.47±2.23
MA6	381.3±3.45	81.67±2.78	66.10±3.27	83.3±1.52	91.23±3.19
MA7	376.7±6.45	82.43±2.51	68.23±1.89	85.21±2.6	94.52±1.67
MA8	369.5±5.36	82.89±1.29	68.98±2.36	84.8±1.93	96.8±2.07

± (Please check this)

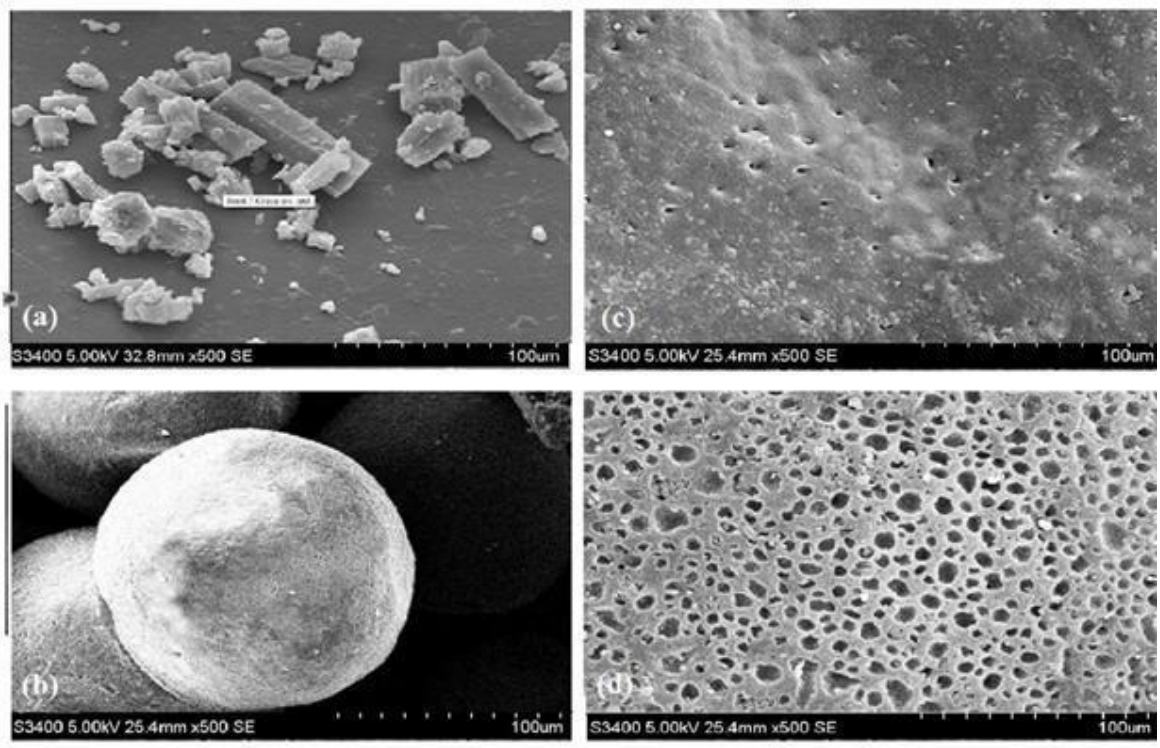

Fig. 1. SEM images of (a) pure drug, (b) intact microsphere (c) surface of microphere (d) cross section of microsphere

hollow microspheres. SEM photographs also indicated the presence of minute pores on the surface of the hollow microspheres due to the evaporation of solvent from the surface (Fig. 1.c) while Fig. 1.d represents the microsphere after dispersion of microspheres in the 0.1 N HCl media.

3.3 Entrapment Efficiency

The entrapment efficiency of the formulated microspheres was in the range of 52.18± 3.84 to 61.01±3.22% (MA1-MA4).There is marked effect of the polymer concentration on the entrapment efficiency of the microsphere (Table 2). The increase in concentration of polymer leads to increased viscosity of the dispersion phase. This tend to increase the diffusion barrier leading to decrease in diffusion of the drug from internal to external phase resulting in higher entrapment efficiency [12]. The concentration of the stabilizer further has a positive effect on the entrapment efficiency of the microsphere which may be due to formation of stable emulsion droplets easily further leading to more microsphere formation and increased entrapment efficiency up to 68.98±2.36%. The study was performed in triplicate.

3.4 Floating Lag Time

Floating lag time of microspheres was found to be 2 minutes.

3.5 Buoyancy

The purpose of preparing floating microspheres was to extend the gastric residence time of a drug. The floating ability test was carried out to investigate the floatability of the prepared microspheres. The microspheres showed good floating ability range from 72.21±1.48% to 84.8±1.93% (for 12 h) as shown in Table 2, (n=3) owing to their hollow nature [13]. The nature of the polymer influenced the floating behaviour of the microspheres. The increase in the concentration of HPMC K4M resulted in enhanced floating ability due to insolubility of the polymer in aqueous solutions [14]. The hydrocolloids like HPMC may entrap some amount of air that also adds to the process of floating.

3.6 *In-vitro* Drug Release Studies

The *in vitro* drug release studies were conducted in 900 ml of simulated gastricfluid (pH 1.2) as a dissolution medium. The percentage drug release study is done for 12hrs using USP Type II dissolution test apparatus at 50 rpm. The *in vitro* drug release profile is shown in the Fig. 2. The studies revealed that all the formulations are showing the sustained release of the drug due to and solubility of HPMC providing passage for the fluid to reach the inner core of microspheres [15]. The concentration of HPMC K4M has significant effect on the release pattern. The maximum % Controlled Drug Release (CDP) was obtained for MA1 (79.41±0.89) and minimum for MA4 (73.13±0.87) keeping the concentration of PVA constant. The result clearly illustrated that there is marked decrease in the % CDP and burst release as the concentration of HPMC was increased. The increased concentration of HPMC also results into increased density of polymer matrix in to the microspheres which results in an increased diffusional path length thus reducing burst effect meanwhile HPMC also provides the channel for diffusion for sustained release of drug as it is soluble in acidic medium [14]. The % CDP of formulations (MA5-MA8) increased with increase in concentration of PVA. The concentration of stabilizer has marked influence on the % CDP as the increase in concentration of PVA resulted in formation of smaller microparticles with greater surface area and subsequently greater % cumulative drug release but after a certain level resulted in burst effect accounting for greater release of drug in the initial phase and inability of the microspheres to sustain the effect for 12 h due to the increased aqueous solubility of PVA as in case of MA8 [16,20].

The release data of all formulations were fitted to different release models namely zero-order, first order, Higuchi model and Peppas model in order to analyze the drug release kinetics and also to identify the mechanism of drug release. The r^2 value is an empirical parameter characterizing the release mechanism. Zero order was considered as the best fitted model with the highest value of coefficient of determination (r^2) in phosphate buffer pH 1.5 (Table 3), which indicates that drug release from the microspheres followed dissolution and diffusion controlled release. Three different release mechanisms can be inferred from the value of r proposed by Korsemeyer and Peppas. The values below 0.43 indicate Fickian diffusion while values in range of 0.43 - 0.85 indicates anomalous non-fickian diffusion and values greater than 0.85 for pure non-fickian diffusion. It was found that the microspheres follow the anomalous non-fickian diffusion [17].

The formulation MA7 was selected as the optimized formulation on the basis of optimum in-vitro buoyancy (85.21±2.6%), entrapment efficiency (68.23±1.89) and maximum % CDR (94.52±1.67) with sustained affect for 12 h. [23]

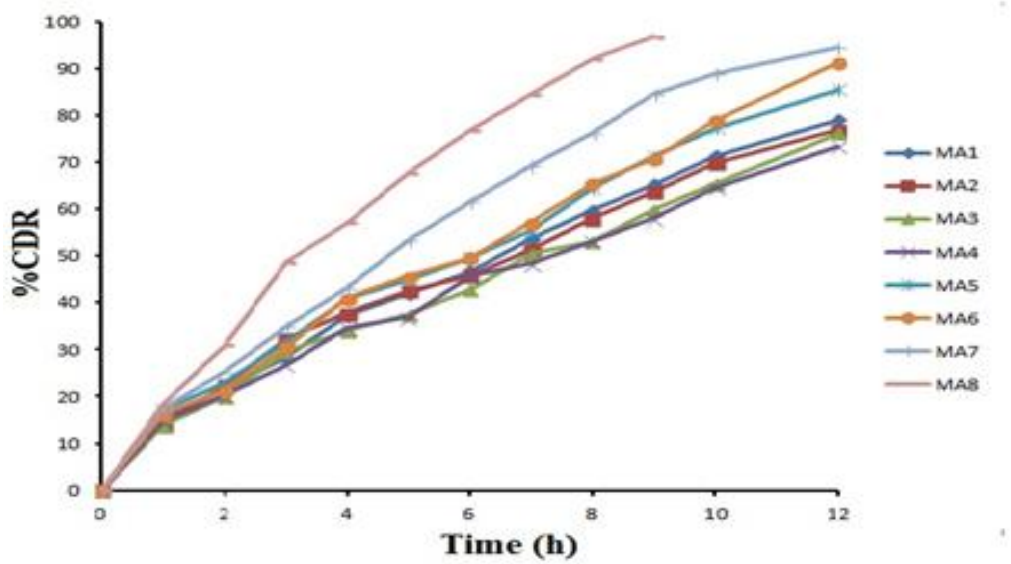

Fig. 2. *In-vitro* release profile of acyclovir microspheres (MA1-MA8)

Table 3. Release kinetics (r^2) data of Acyclovir from floating microspheres

Formulation code	Zero order	First order	Higuchi model	Peppas model (n)
MA 1	0.981	0.602	0.972	0.549
MA2	0.972	0.582	0.978	0.546
MA3	0.982	0.610	0.962	0.556
MA4	0.979	0.604	0.942	0.531
MA5	0.980	0.594	0.969	0.554
MA6	0.988	0.617	0.958	0.488
MA7	0.972	0.601	0.969	0.479
MA8	0.970	0.616	0.973	0.523

3.7 Micromeritic Properties of Optimized Formulation (MA7)

Optimized formulation was evaluated for micromeritic properties such as bulk density, tapped density, Hausner's ratio, Carr's compressibility index and angle of repose in order to check the flow properties of microspheres. The bulk density and tapped density was found to be 0.336±0.040 and 0.372±0.023 gm/cm^3 respectively (Table 4). The reason for estimating above said parameter was to determine the size of the capsule and to analyse the flow behaviour of the microspheres necessary for the formulation development of the microspheres. The parameters are described in Table 4.

Table 4. Micromeritic properties of optimized formulation (MA7) (n =3)

Parameters	Value
Bulk density	0.336 ± 0.040
Tapped density	0.372 ± 0.023
Hausners ratio	1.14 ± 0.06
Carr's compressibility index	11.92 ± 1.87
Angle of repose	21.9 ± 1.39

3.8 The Hausner's Ratio

The Hausner's ratio was found to be 1.16± 0.05 which was less than 1.25 indicating excellent flow properties of the microspheres.

3.9 Carr's Compressibility Index

was determined to be 14.06±1.64% (Table 4.) which lies within the range of (5-15%) also indicates excellent flow of microspheres. The angle of repose of optimized formulation of microspheres was found to be 23.19±2.39°, which was less than (25°) again indicating excellent particle flow. All these results proved that the microspheres were suitable to further pharmaceutical processing steps [18].

3.10 X-ray Diffraction Analysis

The X-ray diffraction is reliable method to evidence the nature of the drug present whether crystalline or otherwise. The inhibited presence of polymers in a formulation and the rigors of formulatory steps usually results in diminution of the crystalline peaks of neat drug and after a combination of drug and polymers emerge closer to the polymer nature. XRD studies of the pure drug ACV, physical mixture of polymer and drug and optimized formulation of microspheres (MA 7) was recorded and then compared (Fig. 3).

The x-ray diffraction profile of the blank microsphere containing HPMC K4M indicated the presence of a completely amorphous material; pure ACV drug showed the classical peaks indicating the crystalline nature of drug. The peaks were depressed in the microspheres. No major difference in the XRD patterns of the blank microsphere and the drug loaded microspheres was noticed indicating the loss of crystalline nature of the drug.

3.11 Conventional Capsule vs. Microspheres

The optimized capsules of ACV microspheres (MA7) were compared with marketed formulation as shown in Fig. 4 for % cumulative drug release. It can be clearly observed that the IR capsule released 100% of the drug within 3 h while the microspheres had released the drug for the period of 12 h fulfilling the objective of sustained release of ACV leading to enhanced oral bioavailability and reduced dosing frequency. [19].

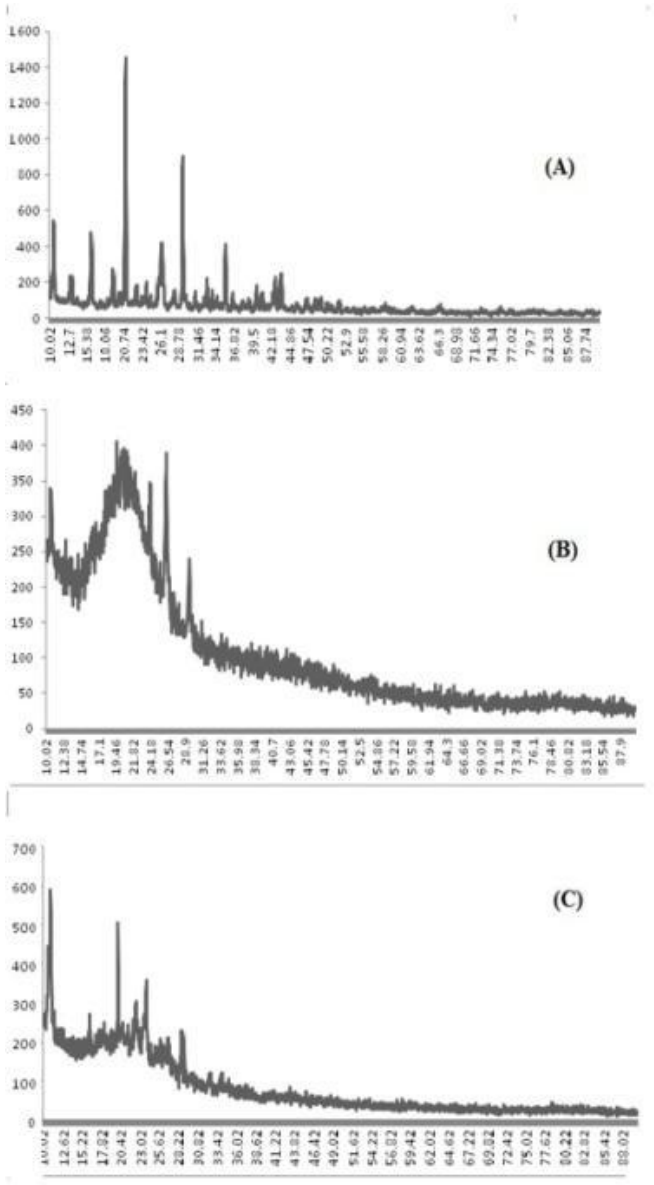

Fig. 3. XRD diffractogram of (a) Acyclovir, (b) Blank microspheres, (c) drug loaded microspheres

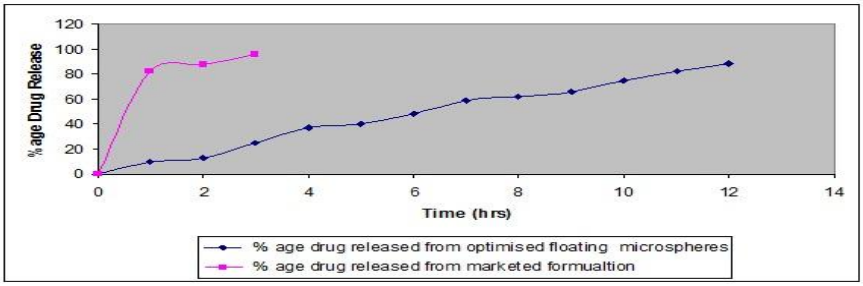

Fig. 4. Comparison of *in vitro* release of optimized microspheres of acyclovir with the marketed formulation of acyclovir IR capsules

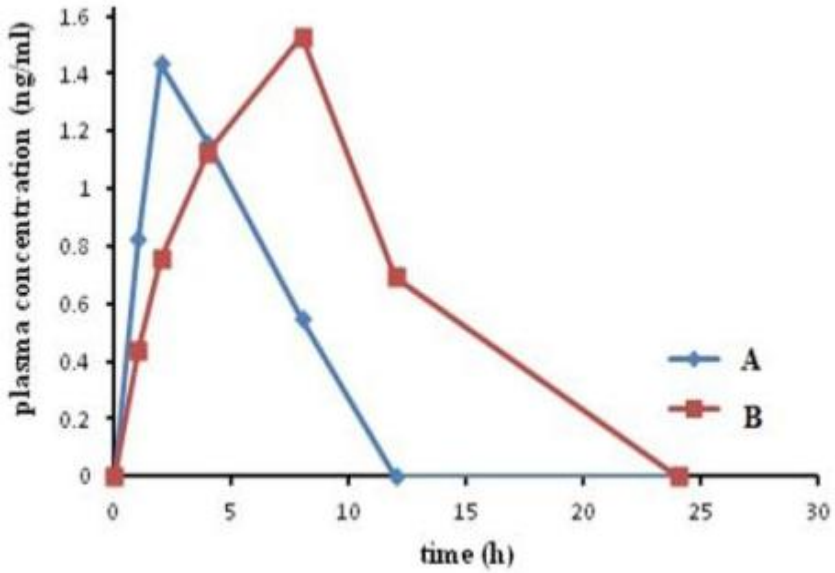

Fig. 5. Plasma concentration time profile of acyclovir after oral administration as- (A) solution of acyclovir; (B) acyclovir microspheres (MA7)

Table 5. Pharmacokinetic parameters of different formulations containing acyclovir after oral administration (mean ± SD, n = 3)

Formulation	t_{max} (hrs)	C_{max} (ng/ml)	AUC $_{0-t}$ (ng.h/ml)	Rel.BA %
Drug solution	2±1.32	1434.29±1021.32	7552.33±3219.09	--
Acyclovir microsphere (MA7)	8±0.92	1582.7±2493.29	12466.21±7974.77	165.17

3.12 Pharmacokinetic Study

The plasma concentration time profile curve of Acyclovir solution and microspheres (MA7) demonstrated the fact that microspheres efficiently released the drug with sustained effect so that the maximum plasma concentration is reached at the end of 8 h while the Acyclovir solution achieved maximum plasma concentration at the end of 3 h as shown in above Fig. 5.

Nearly two times higher AUC (0–24) value of ACV for these microspheres as compared to drug solution (7552.33±3219.09 ng.h/ml) was observed as shown in above Table 5. In addition, ACV microspheres showed the ability to maintain the ACV plasma concentration through 8 h as compared to the drug solution that could maintain this level of drug only for 4 h. These results confirmed the sustained release potential of floating microspheres of ACV prepared from HPMC K4M polymer. Hence, the overall better pharmacokinetic performance of floating microsphere of ACV in comparison to drug solution is due to increased residence time within upper GI tract [21,22].

4. CONCLUSION

Microspheres formulated with HPMC by solvent evaporation method were able to float for a period of 12 h. The increase in the concentration of HPMC K4M resulted in enhanced floating ability due to insolubility of the polymer in aqueous solutions. SEM studies revealed the presence of pores on floating microspheres due to matrix erosion, which are responsible for the floating ability. The X- ray diffraction studies demonstrate that the drug is present in the amorphous form in the microspheres. The microspheres efficiently released the drug with sustained effect and the maximum plasma concentration was reached at the end of 8 h. The floating microspheres were able to sustain the drug release over a period of 8 h. The above

results revealed the possibility of development of floating drug delivery system using HPMC polymer blend for sustained and local delivery of the ACV in the stomach resulting into overall enhanced bioavailability.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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