International Journal of Applied Pharmaceutics
Vol 2, Issue 3, 2010

Research Article

PREPARATION AND CHARACTERIZATION OF FLOATING DRUG DELIVERY SYSTEM OF ACYCLOVIR

GUPTA S. K.[1], GUPTA UDIT[2], OMRAY L. K.[3*], YADAV REETESH[4], SONI V. K.[4]

[1]Chandrashekhar Singh College of Pharmacy, Kaushambi, Allahabad, (U. P.), India; [2]Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Erandwane, Pune-411038, Maharashtra State, India; [3]Sagar Institute of Pharmaceutical Sciences, Sironja, Sagar (M.P.) - 470228, India; [4]Shri Ram Institute of Technology (Pharmacy), Jabalpur, 482003, (M.P.), India E-mail: lkomray@rediffmail.com

Received: 25 March 2010, Revised and Accepted: 24 April 2010

ABSTRACT

Present investigation deals with the preparation and characterization of floating drug delivery system (FDDS) of acyclovir containing polyvinyl pyrrolidon (PVP), polyvinyl alcohol (PVA) and hydroxy propyl methyl cellulose (HPMC) as the polymers and sodium bicarbonate as a gas generating agent, to reduce floating lag time. The FDDS tablets were prepared by wet granulation method. Five formulations were developed which differed in the ratio of polymers. Formulations AV1, AV2, AV3, AV4, and AV5 were composed of PVP, PVA and HPMC in the ratio of 1:1:1, 2:1:1, 3:1:1, 4:1:1 and 5:1:1 respectively. All the formulations were evaluated for hardness, friability, weight variation, drug content uniformity, buoyancy studies, swelling index and *in vitro* drug release study. Estimation of acyclovir in the prepared FDDS was carried out by extracting drug in double distilled water and measuring the absorbance at 256 nm. *In vitro* drug release study was performed using United State Pharmacopoeia (USP) 23 type 2 dissolution test apparatus employing paddle stirrer at 50 rpm using 900 mL of double distilled water maintained at 37ºC ± 0.5ºC as the dissolution medium. On the basis of evaluation parameter formulation AV4 selected as developed formulation. Therefore, it can be concluded that the FDDS may be exploited successfully for the delivery of drugs such as acyclovir.

Keywords: Gastro retentive drug delivery, Tablets, Sustained drug delivery, *In vitro* drug release

INTRODUCTION

Oral delivery of drug is the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc[1]. Conventional drug delivery systems achieve as well as maintain the drug concentration within the therapeutically effective range needed for treatment only when taken several times a day. This results significant fluctuations in drug levels[2]. Several technical advancements have led to the development of many novel drug delivery systems (NDDS) that could revolutionize method of medication and provide a number of therapeutic benefits. The most important objectives of these NDDS are: (a) preferably a single dose for the whole duration of treatment. (b) Site specific drug delivery, thus minimizing or eliminating side effects[3].

Presently, to develop a single dose therapy for the whole duration of the treatment has focused attention on controlled or sustained drug delivery systems. Sustained release describes a drug delivery system with delayed and/or prolonged release of drug. It also implies delayed therapeutic action and sustained duration of therapeutic effect whereas controlled release implies a predictability and reproducibility in the drug release kinetics[4,5]. In other words, sustained release dosage forms provide medication over an extended time period whereas controlled release systems attempt to control drug concentration in the target tissue.

FDDS is one of the most accepted sustained NDDS. The FDDS can be retained in the stomach and assists in improving the oral sustained delivery of drugs that have an improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Several approaches are currently used to prolong gastric retention time. These includes floating drug delivery systems, swelling and expanding systems, polymeric bioadhesive systems, high density systems, and other delayed gastric emptying devices[6].

During the last decade, many studies have been performed concerning the sustained release dosage form of drugs, which have aimed at the prolongation of gastric emptying time (GET). The GET has been reported to be from 2 to 6 hours in humans in the fed state[7]. Accordingly, when a sustained release dosage form is administered orally, sufficient bioavailability and prolongation of the effective plasma level occasionally can not be obtained. Also reflected in the recent scientific patent literature, an increased interest in novel dosage forms which possesses not only a mechanism for controlled release of the drug but also controlled gastrointestinal transit time exists today in academic and industrial research groups[8].

Acyclovir is a guanine analogue antiviral drug used for the treatment of herpes simplex virus. Its oral bioavailability is 10-20% with a plasma elimination half life of 1-2 hours[9]. Acyclovir has absorption window in duodenum and small intestine[10]. After peroral administration the bioavailability of acyclovir is only 20% compared to intravenous route, remaining 80% of the drug can be detected in the faeces. After repeated peroral dosing of small amounts of acyclovir the bioavailability can be enhanced[11,12]. These facts indicate that the drug is only absorbed from the upper part of gastrointestinal tract (GIT) and increasing its gastric residence time may enhance bioavailability of acyclovir. Therefore, acyclovir is selected as a model drug for the design of a FDDS with a view to improve its oral bioavailability.

Present investigation deals with the preparation and characterization of floating drug delivery system of acyclovir containing polyvinyl pyrrolidon, polyvinyl alcohol and hydroxy propyl methyl cellulose as the polymers and sodium bicarbonate as a gas generating agent, to reduce floating lag time. The FDDS tablets were prepared by wet granulation method. Five formulations were developed which differed in the ratio of polymers. Formulations AV1, AV2, AV3, AV4, and AV5 were composed of PVP, PVA and HPMC in the ratio of 1:1:1, 2:1:1, 3:1:1, 4:1:1 and 5:1:1 respectively.

MATERIALS AND METHODS

Materials

Acyclovir was received as a gift sample from Modern Labs (Indore, India). HPMC K4M was received as a gift sample from Colorcon Asia Pvt Ltd (Goa, India). Poly vinyl pyrollidone K30 (PVP K30), Polyvinyl alcohol and sodium bicarbonate were purchased from S. D. Fine Chemicals (Mumbai, India). All other ingredients were of laboratory grade.

Methods

Prepration of FDDS

All the ingredients were accurately weighed and sieved through sieve no. 60. In order to mix the ingredients thoroughly, drug and all the excipient except the lubricants (magnesium stearate and talc) were blended geometrically in mortar and pestle for 15 minutes and granulated using (polyvinyl pyrrolidon) PVP K30 dissolved in sufficient isopropyl alcohol by passing through sieve no.12. Granules were dried at 45°C for 4 h. The dried granules were sized through sieve no. 18 and lubricated by adding magnesium stearate and talc. Tablets were compressed on a single punch tablet machine using flat surfaced, round shaped punches of 12 mm diameter[13]. Hardness of the tablets was maintained around 5 kg/cm^2.

Characterization of fdds

Hardness and friability test

The crushing strength (Kg/cm^2) of tablets was determined by using Monsanto type hardness tester[14]. Friability was determined by weighing 10 tablets after dusting, placing them in the friabilator (Roche Friabilator) and rotating the plastic cylinder vertically at 25 rpm for 4 min[15]. After dusting, the total remaining weight of the tablets was recorded and the percent friability (PF) was calculated using formula PF = ($Weight_{original}$ – $Weight_{final}$) / $Weight_{original}$ X 100.

Uniformity of weight and drug content

Uniformity of weight was determined with the help electronic balance. Uniformity of drug content was determined by taking 5 tablets in a glass mortar and powdered; 100 mg of this powder was placed in a 100 mL stoppard conical flask[15]. The drug was extracted in double distilled water with vigorous shaking on a mechanical shaker (100 rpm) for 5 hours and filtered into 50 mL volumetric flask through cotton wool and filtrate was made up to the mark by double distilled water through filter, further appropriate dilution were made and absorbance was measured at 256nm using double distilled water as blank solution by UV-Visible double beam spectrophotometer (EI, India) [16].

Buoyancy studies

The *in vitro* buoyancy was characterized by floating lag time and total floating time. The test was performed using a USP 23 type-2 dissolution test apparatus (Electrolab) using 900 mL of double distilled water at paddle rotation of 50 rpm at 37ºC ± 0.5ºC. The time required for the tablets to rise to the surface of the dissolution medium and the duration of time the tablets constantly floated on the dissolution medium were noted as floating lag time and floating time, respectively[6].

Swelling Index

The individual tablets were weighted accurately and kept in 50 mL of double distilled water. Tablets were taken out carefully after 60 minutes, blotted with filter paper to remove the water present on the surface and weighed accurately[17]. Percentage swelling index (SI) was calculated by using the formula SI = (Wet weight – Dry Weight / Dry weight) X 100.

***In vitro* dissolution study**

In vitro dissolution study of FDDS of acyclovir were carried out in USP 23 type 2 dissolution test apparatus (Electrolab), employing a paddle stirrer at 50 rpm using 900 mL of 0.1N HCL as dissolution medium, at 37ºC ± 0.5ºC as dissolution medium. One tablet was used in each test[17]. The dissolution profile of all the batches was fitted to zero-order (Eq. 1), first-order (Eq. 2), Higuchi (Eq. 3), and Korsemeyer-peppas (Eq. 4) models to ascertain the kinetic modeling of drug release[18].

$$R = k_1 t \quad (1)$$

$$\log UR = \frac{k_2 t}{2.303} \quad (2)$$

$$R = k_3 t^{0.5} \quad (3)$$

$$R = k_4 t^n \quad (4)$$

Where R and UR are the released and unreleased percentages, respectively, at time (t); k_1, k_2, k_3, and k_4 are the rate constants of zero order, first order, Higuchi matrix, and Peppas-Korsmeyer model, respectively.

RESULTS AND DISCUSSION

FDDS of acyclovir were developed using various proportions of PVP, PVA and HPMC as the polymers. Sodium bicarbonate used as a gas generating agent, to reduce floating lag time. The FDDS tablets were prepared by wet granulation method. Five formulations were developed which differed in the ratio of polymers. Formulations AV1, AV2, AV3, AV4, and AV5 were composed of PVP, PVA and HPMC in the ratio of 1:1:1, 2:1:1, 3:1:1, 4:1:1 and 5:1:1 respectively (Table 1). The evaluation parameter (Table 2) such as hardness were in the range of 4.2 to 5.4 Kg/cm^2, The friability of all tablets were less than 1% i.e. in the range of 0.62 to 0.79%. The percentage deviations from the mean weights of all the batches of prepared FDDS were found to be within the prescribed limits of Indian Pharmacopoeia. The average drug contents were found between 98.51 to 101.84%. The floating lag time was found to be in between 121 to 182 second with a floating time of 24 hours. The swelling index was found to be in the range of 41.43 to 69.16. *In vitro* dissolution study of FDDS of acyclovir was carried out in USP 23 type 2 dissolution test apparatus, employing a paddle stirrer at 50 rpm using 900 mL of 0.1N HCL as dissolution medium, at 37ºC ± 0.5ºC. One tablet was used in each test at predetermined time interval; 5 mL of the samples were withdrawn by means of a syringe fitted with a prefilter. *In vitro* dissolution results (Fig. 1) were 63.54 to 71.56% in 8 h, this may be due to the composition of FDDS.

Table 1: Composition of FDDS formulations

Ingredient	AV1	AV2	AV3	AV4	AV5
Acyclovir (mg)	400	400	400	400	400
PVP (mg)	66.66	100	120	133.33	142.85
PVA (mg)	66.66	50	40	33.33	28.57
HPMC (mg)	66.66	50	40	33.33	28.57
Sodium bicarbonate (mg)	75	75	75	75	75
Magnesium stearate (mg)	6.5	6.5	6.5	6.5	6.5
Talc (mg)	6.5	6.5	6.5	6.5	6.5

Table 2: Evaluation of FDDS formulations

Formulation Code	Hardness Kg/ cm^2	Friability % W/W	Average weight (mg)	Drug content %	Swelling index	Floating Lag time (Sec)	Floating time (hrs)
AV1	4.8	0.69	676	98.51	45.48	181	24
AV2	5.4	0.79	681	100.84	69.16	126	24
AV3	4.2	0.68	671	99.65	54.17	124	24
AV4	4.9	0.62	679	99.31	41.43	121	24
AV5	4.5	0.65	691	101.22	56.05	182	24

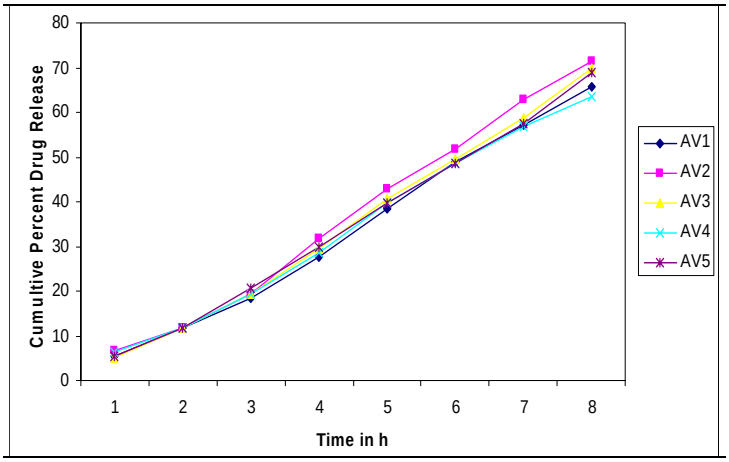

Fig. 1: *In vitro* drug release study of formultions AV1 to AV5

The release mechanism of acyclovir from these floating formulations was also evaluated on the basis of theoretical dissolution equations including zero-order, first-order, Higuchi matrix and Peppas-Korsmeyer kinetic models. The regression coefficients and rate constants from *in vitro* release profiles of acyclovir in 0.1 N HCL were calculated using PCP Disso Version 3 software (Pune, India) and are reported in Table 3. Release pattern of acyclovir from all floating formulations followed zero-order model, which may be due to the composition of the formulations.

Table 3: The regression coefficients and rate constants for *in vitro* release study of floating drug delivery systems.

Formulation	Zero-order model		First-order model		H-M model		P-K model	
	r	k1	r	k2	r	k3	r	k4
AV1	0.9786	14.5673	0.8734	-0.1278	0.9793	11.6841	0.9609	16.0981
AV2	0.9865	15.5763	0.8799	-0.1296	0.9809	11.2426	0.9698	17.1516
AV3	0.9914	15.8942	0.8845	-0.1134	0.9838	12.2837	0.9787	18.0139
AV4	0.9985	16.5382	0.8839	-0.1243	0.9823	12.4262	0.9702	18.5191
AV5	0.9934	16.2583	0.8799	-0.1219	0.9798	12.2847	0.9796	18.2749

*H-M, indicates Higuchi matrix; P-K, Peppas-Korsmeyer; r, indicates correlation coefficient; k1-k4, rate constants of zero-order, first-order, Higuchi matrix, Peppas-Korsmeyer; AV1 to AV5 different floating drug delivery systems.

CONCLUSION

Preparation of FDDS of acyclovir containing, PVP, PVA and HPMC as the polymers and sodium bicarbonate as a gas generating agent is easy and economic. It can also be scale up for commercial purpose. Evaluation procedures are also easy and require usual laboratory equipments. On the basis of physicochemical parameters and *in vitro* release study, formulation AV4 was found to be better than among five formulations and it was selected as the optimized formulation. Therefore, it can be concluded that the FDDS may be exploited successfully for the delivery of drugs such as acyclovir.

REFERENCES

1. Patil JM, Hirlekar RS, Gide PS, Kadam VJ. Trends in floating drug delivery systems. J Sci Ind Res 2006;65 :1-21.
2. Kumar R, Philip A. Gastroretentive dosage forms for prolonging gastric residence time. Int J Pharm Med 2007;21 :157-171.
3. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: a review. AAPS PharmSciTech 2005;6 :E372-E390.
4. Chavanpatil MD, Jain P, Chaudhari S, Shear R, Vavia PR. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. Int J Pharm 2006;316 :86-92.
5. Chien YW. Rate-control drug delivery systems: controlled release vs sustained release. Med Prog Technol 1989;15 :21-46.
6. Patel VF, Patel NM. Intragastric floating drug delivery system of cefuroxime axetil: In vitro evaluation. AAPS PharmSciTech 2006;7 :E1-E7.
7. Kumar R, Philip A. Gastroretentive dosage forms for prolonging gastric residence time. Int J Pharm Med 2007;21 :157-171.
8. Yeole PG, Khan S, Patel VF. Floating drug delivery systems: need and development. Indian J Pharm sci 2005;67 :265-272.
9. Sweetman SC (Ed.), Martindale, The Complete Drug Reference, 33th ed., Pharmaceutical Press. London, 2002; p.612.
10. Groning R, Berntgen M, Geogarakis M. Acyclovir serum concentrations following peroral administration of magnetic depot tablets and the influence of extra corporal magnet to control gastrointestinal transit. Eur J Pharm Biopharm 1996;46 :285-291.
11. Lewis L, Fowle A, Bittiner S, Bye A, Isaacs P. Human gastrointestinal absorption of acyclovir from tablet, duodenal infusion and sipped solution. Br J Clin Pharmacol 1986;21 :459-462.
12. Vergin H, Kikuta C, Mascher H, Metz R. Pharmacokinetics and bioavailability of different formulations of acyclovir. Arzneim Forsch 1995;45 :508-515.
13. Dave BS, Amin AE, Patel MM. Gastroretentive drug delivery system of ranitidine HCl: Formulation and *in vitro* evaluation. AAPS PharmSciTech 2004;5 :Article 34.
14. Banker GS, Anderson NR. Tablets. In: Lachman L, Liberman HA, Kanig JL, eds. The Theory and Practice of Industrial

Pharmacy, Mumbai, India, Varghese Publishing House, 3rd Edition. 1991 :297-303.

15. Rosa J-C M, Zia H, Christopher Rhodes. Design and testing in vitro of bio-adhesive and floating drug delivery systems for oral application. Int. J. Pharm 1994;105 :65-70.
16. Gandhi P, Momin N, Kharade S, Konapure NP, Kuchekar BS. Spectrophotometric estimation of acyclovir in pharmaceutical dosage forms. Indian J Pharm sci 2006;68 :516-517.
17. Chavanpatil MD, Jain P, Chaudhari S, Shear R, Vavia PR. Development of sustained release gastrorentantive drug delivery system for ofloxacin: *in vitro* and *in vivo* evaluation. Int J Pharma 2005;304 :178-184.
18. Jain SK, Agrawal GP, Jain NK. Evaluation of porous carrier-based floating orlistat microspheres for gastric delivery. AAPS PharmSciTech 2006;7 :E1-7.