A HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC METHOD FOR DETERMINATION OF VALACYCLOVIR IN PHARMACEUTICAL DOSAGE FORMS AND RAT PLASMA

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ABSTRACT

A simple, high performance liquid chromatographic method has been developed for the determination of valacyclovir in pharmaceutical dosage forms and rat plasma. The elution was performed using different mobile phase mixture of acetonitrile: methanol in ratio of 15:85 for pharmaceutical dosage form and acetonitrile: methanol: water in the ratio of 12:44:44 for plasma samples at a flow rate of 1.2 ml min-1 on a Phenomenex C18 column (150 × 4.6 mm, i.d., 5µm) at ambient temperature. The drugs were monitored at a wavelength of 260 nm and were separated within 10 min. Marketed formulations were prepared in suitable dilutions and plasma samples were prepared by precipitating proteins with the help of 25% perchloric acid. The method was successful in detecting the drugs at a concentration of less than 0.05 ìg/ml. %RSD for intra- and inter-day studies was found to be within 8.83% for all the selected concentrations. Moreover, the method was validated as per ICH guidelines and the results were found to be within the acceptable range. Hence, the proposed method can be used for the routine quality control of the drugs and can also be applied to pharmacokinetic studies.

KEYWORDS : Valacyclovir, Reverse phase HPLC, Validation, Rat plasma

INTRODUCTION

Valacyclovir [1] (Fig. 1) is L-Valyl ester (9-[(2-hydroxy ethoxy) methyl] guanine hydrochloride),

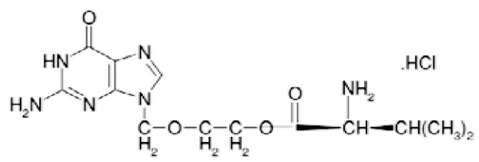

Figure 1 : Structure of valacyclovir

of acyclovir, after oral administration is rapidly converted into acyclovir which shows antiviral activity against herpes simplex virus type I (HSV-1) and (HSV-2), Varicella Zoster Virus (VZV). Acyclovir oral bioavailability was increased when administered in the form of valacyclovir [2] and valacyclovir (VCV) rapidly converted to Acyclovir (ACV) *in vivo* which inhibits DNA synthesis. Valacyclovir is available as tablet dosage form in market and few HPLC [3-5] methods were reported for the estimation of valacyclovir in pharmaceutical formulations and in biological fluids [6] and one of spectrophotometric [7] method were also reported. There are two stability indicating HPLC [8, 9] methods were developed for valacyclovir, Several studies have reported HPLC determination of ACV in different matrices *viz.* pharmaceuticals [10–14], human plasma [15–20], serum [21] and maternal plasma, amniotic fluid, fetal and placental tissues [22]. High-performance capillary electrophoresis has also been used for the determination of ACV (acyclovir) in urine [23] and plasma [24]. A sensitive assay is reported by

Jin et al. [25] to determine ACV in aqueous humor by LC–MS. The response was linear over the concentration range of 5–50ng/ml. Recently a quantitative determination of ACV in plasma has been done by near-infrared spectroscopy [26]. A sensitive and selective LC–MS/MS method based on hydrophilic interaction liquid chromatography has been reported for the determination of ACV in pregnant rat plasma and tissues [27] but the reported methods were having disadvantages like high flow rate and high retention time and more organic phase and the aqueous phase is not compatible to LC-MS analysis. The simultaneous estimation of these drugs in biological samples has been the subject of very few reports due to structural similarity of VCV (valacyclovir) and ACV with the endogenous components. Weller's HPLC method [28], proposes a gradient mobile phase for their simultaneous measurement in plasma. Pham-Huy et al. [29] have developed a simple and specific HPLC–UV assay for VCV and ACV in human serum, urine and dialysis liquids. The lower limits of quantification were 250 and 200 ng/ml for VCV and ACV respectively and the chromatographic run time was 12 min. Recently a selective and rapid liquid chromatography/negative-ion electrospray ionization mass spectrometry method has been reported for the quantification of VCV and its metabolite in human plasma [30]. A thorough and complete method validation of VCV in rat plasma was done following the USFDA guidelines [31]. The analytes were separated on a reversed-phase porous graphitized carbon column with a short analytical run time of 4 min. The proposed HPLC method utilizes economical solvent system as compared with the previous reported methods and is compatible with LC-MS analysis. The proposed HPLC method leads to better retention time, very sharp and symmetrical peak shapes. The aim of the study was to develop a simple, precise and accurate reverse-phase HPLC method for the estimation of valacyclovir in bulk drug samples, in pharmaceutical dosage forms and rat plasma which can be effectively applied for the pharmacokinetic study of the drug valacyclovir.

EXPERIMENTAL SECTION

Chemicals and Reagents

Valacyclovir was obtained from Actavis Pharmaceutical Ltd., Chennai, India. Acetonitrile, Methanol and Water (obtained from Merck chemicals, Worli, Mumbai, India.) of HPLC grade were used. All the other reagents (70% perchloric acid) used were of Development and Validation of RP-HPLC Method for Determination of Valacyclovir was of analytical grade are also obtained from Merck chemicals, Worli, Mumbai, India. Pharmaceutical formulations were purchased from Cipla Pharmacy.

Instrumentation and chromatographic conditions

A high-performance liquid chromatography (Shimadzu, Kyoto, Japan) was composed of a LC-20AT Prominence solvent delivery module, a manual rheodyne injector with a 20-µl fixed loop and a SPD-20A Prominence UV–visible detector. Separation was performed on a Phenomenex C18 column (particle size 5µm; 250mm□4.6mm i.d.; Phenomenex, Torrance, USA) at an ambient temperature. The data acquisition was made by Spinchrom Chromatographic Station® CFR Version 2.4.0.195 (Spinchrom Pvt. Ltd., Chennai, India). The mobile phase consisted of acetonitrile: methanol in ratio of 15:85 for pharmaceutical dosage form and acetonitrile: methanol: water in the ratio of 12:44:44 for plasma samples at a flow rate of 1.2 ml min-1.

Preparation of stock and standard solutions

Stock solution of 1mg/ml valacyclovir was prepared in methanol. Standard solution of valacyclovir was prepared by mixing and diluting the appropriate amounts from the individual stock solution. The final concentrations of the standard solution were 1000, 900, 700, 500, 300, 100, 50, 25, 2.5 and 0.5µg/ml. Precision and accuracy standards with concentrations of 900, 100, 25 and 0.5µg/ml were also prepared in the same manner. Stock solutions were refrigerated when not in use and replaced on bi-weekly basis. Fresh standard solutions were prepared for each day of analysis or validation. For the analysis of pharmaceutical formulations, ten tablets of valacyclovir were weighed and powdered individually. The mixture of formulations was prepared by weighing amount equivalent to labeled claim from the powdered formulations. To this, a suitable amount of methanol was added. The mixture was subjected to sonication for 30 min for a complete extraction of the drugs, and then filtered through 0.2µm filter paper and diluted with methanol at a suitable concentration range (15mcg/ml) and injected into HPLC system for the analysis.

Calibration curves

Pure drug calibration curve were prepared by mixing 20µl of the above standard solutions and diluting it up to 200µl by methanol to obtain calibration curve range of 0.05-100µg/

ml. Plasma calibration points were prepared by spiking 200µl of rat plasma with 20µl of above prepared valacyclovir standard solutions. The calibration curves for rat plasma were in the range of 0.05-100µg/ml. After each matrix was spiked, it was subjected to further sample preparation before analysis.

Sample preparation

The ten samples containing plasma spiked with valacyclovir of different concentration was taken in 1.5ml micro-centrifuge tubes. To each 200µl of sample was mixed with 45µl of 25% perchloric acid for 30 seconds. The samples were centrifuged at 1200 g for 15min. 20µl of clear supernatant liquid was transferred in Hamilton Syringe and injected into HPLC system for analysis.

Sample collection

The use of animals in this study was approved by GTU (Gujarat Technological University, Ahmadabad, Gujarat, India) and CPCSEA (Committee for the Purpose of Supervision on Experimental Animals). The rats were housed one animal per cage in Sigma Institute of Pharmacy animal house. The environment was controlled with daily feeding and water.

Blood samples were collected in 2ml micro-centrifuge tube from retro orbital plexus of albino rats. The 2ml micro-centrifuge containing blood was centrifuged at 15000 rpm for 15 min and the plasma was collected carefully. Blood sample was collected on regular basis from different rats and plasma was separated till the study is been completed so that the analysis is unbiased in nature.

RESULTS AND DISCUSSION

Optimization of chromatographic conditions

The drugs were soluble in organic solvents like methanol and acetonitrile. During the development phase, the mobile phase containing methanol-water in different ratios and methanol-buffer solution resulted in peaks with poor resolution and the acetonitrile-methanol-water and acetonitrile-methanol resulted in good resolution of peaks. The successful use of both acetonitrile and methanol along water reduced tailing and resulted in good peak symmetry and resolution. The optimized mobile phase contained acetonitrile: methanol in ratio of 15:85 for pharmaceutical dosage form and acetonitrile: methanol: water in the ratio of 12:44:44 for plasma samples flow rate of 1.2 ml min-1. The analytes were monitored at 260 nm and the retention times were found to be 2.0min for valacyclovir in both the mobile phases, respectively. (Fig. 2, 3 and 4)

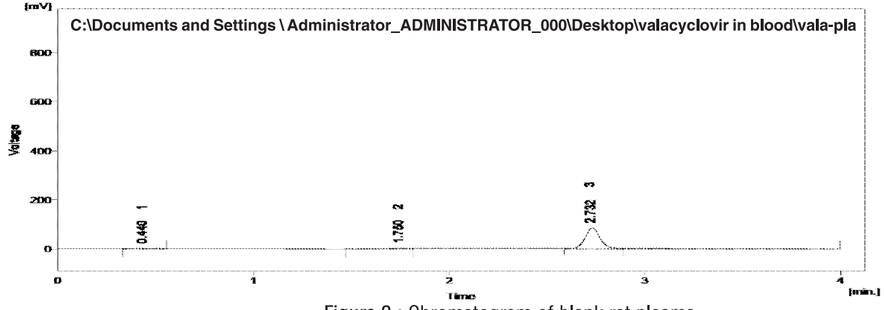

Figure 2 : Chromatogram of blank rat plasma

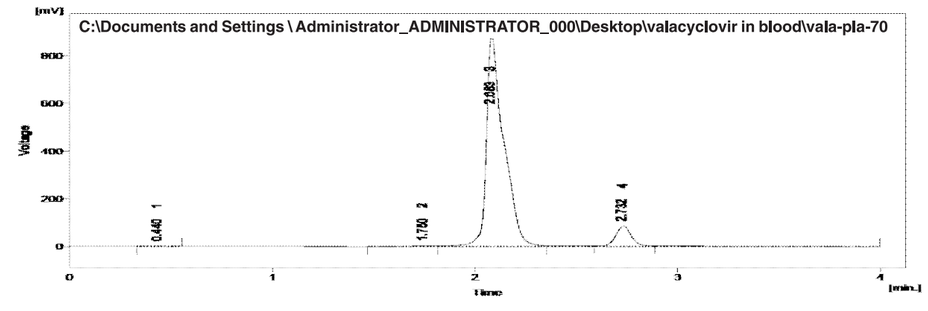

Figure 3 : Chromatogram of Valacyclovir in rat plasma 70mcg/ml

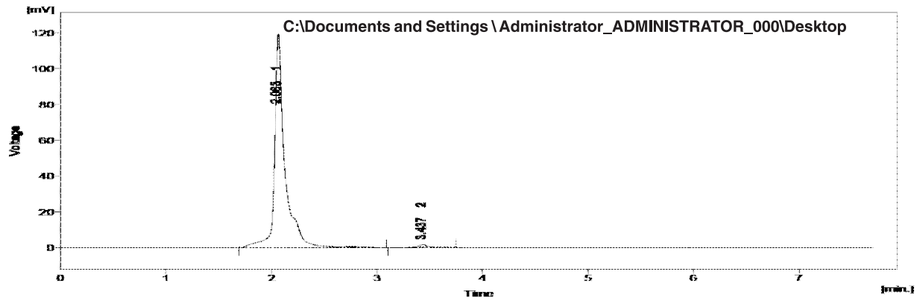

Figure 4: Chromatogram of Pure Valacyclovir in methanol 30mcg/ml

1. Validation of the developed method

The proposed method was validated as per the guidelines in ICH for its linearity, accuracy, precision, specificity and selectivity, robustness and stability *etc*.

2. Linearity : The linearity was tested for the concentration range of 100, 90, 70, 50, 30, 10, 5, 2.5, 0.25 and 0.05µg/ml the calibration curve was constructed and evaluated by its correlation coefficient. The equation for plasma is Y= 82.09X + 56.90 and the equation for pure drug is Y= 38.22X + 3.598. (Table 1 & Fig. 5 & 6)

Table 1: Linear regression equations generated from validation for each matrix: Slope, Intercept and Coefficient of determination

Analyte	Matrix	Nominal concentration (µg/ml)	Mean Concentration Found (µg/ml)	S.D.	Precision (%RSD)	Mean accuracy (%)
Valacyclovir	Pure drug in plasma	Intra-day				
		90	90.272	0.707805	0.784080	100.201
		10	10.084	0.436433	4.32	100.84
		2.5	2.53733	0.153221	6.038	101.49
		0.05	0.052	0.003356	6.45	104
		Inter-day				
		90	90.466	0.70734	0.78188	100.417
		10	9.798	0.383627	3.915	97.98
		2.5	2.594	0.187697	7.23	103.76
		0.05	0.0516	0.004561	8.83	103.2
	Pure drug in methanol	No. of Preparations	Amount Added		Recovery (%)	
		S1:80%	10	8	100.25	
		S2:80%	10	8	101.75	
		S3:80%	10	8	101.5	
		S1:100%	10	10	101	
		S2:100%	10	10	100.5	
		S3:100%	10	10	101.2	
		S1:120%	10	12	99.54	
		S2:120%	10	12	97.87	
		S3:120%	10	12	100.793	

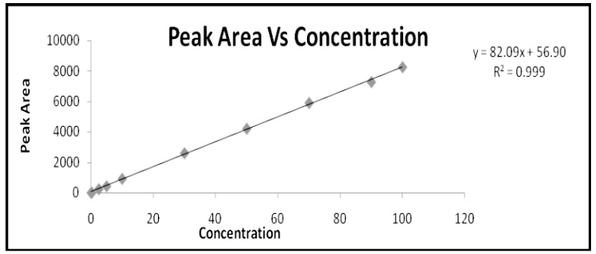

Figure 5: Calibration curve of pure valacyclovir in methanol

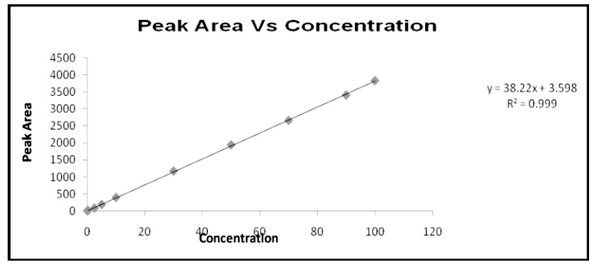

Figure 6: Calibration curve of pure valacyclovir in rat plasma

3. Accuracy : The accuracy of a method is expressed as the closeness of agreement between the value found and the value that is accepted as a reference value. It is determined by calculating the percent difference (%bias) between the measured mean concentrations and the corresponding nominal concentrations. The accuracy of the proposed method was tested by recovery experiments by adding known amounts of valacyclovir corresponding to 80, 100 and 120% of the label claim from the respective standard solution. The accuracy was then calculated as the percentage of valacyclovir recovered by the assay (Table 2). The precision of the proposed method was assayed by replicate injections of valacyclovir.

Table 2: Accuracy Data Obtained by Recovery Studies of valacyclovir in plasma and adding pure valacyclovir 80%, 100% and 120% in methanol.

Analyte	Matrix	Nominal concentration (µg/ml)	Mean Concentration Found (µg/ml)	S.D.	Precision (%RSD)	Mean accuracy (%)
Valacyclovir	Pure drug in plasma	Intra-day				
		90	90.272	0.707805	0.784080	100.201
		10	10.084	0.436433	4.32	100.84
		2.5	2.53733	0.153221	6.038	101.49
		0.05	0.052	0.003356	6.45	104
		Inter-day				
		90	90.466	0.70734	0.78188	100.417
		10	9.798	0.383627	3.915	97.98
		2.5	2.594	0.187697	7.23	103.76
		0.05	0.0516	0.004561	8.83	103.2
	Pure drug in methanol	No. of Preparations	Amount Added		Recovery (%)	
		S_1:80%	10	8	100.25	
		S_2:80%	10	8	101.75	
		S_3:80%	10	8	101.5	
		S_1:100%	10	10	101	
		S_2:100%	10	10	100.5	
		S_3:100%	10	10	101.2	
		S_1:120%	10	12	99.54	
		S_2:120%	10	12	97.87	
		S_3:120%	10	12	100.793	

4. Precision: The method was validated using four QC point for each calibration curve. Five replicates of each QC points were analyzed every day to determine the intra-day precision. This process was repeated three times over three days in order to determine the inter-day precision. The concentration of the QC points for plasma and pure drug were 90, 10, 2.5 and 0.05µg/ml. (Table 3)

Table 3: Inter-day (n=5) and Intra-day (n=5) precision (%R.S.D.) measured for QC points for valacyclovir from plasma and pure drug.

	T.C. Conc.	Day 1		Day 2		Day 2		Inter-day	
Plasma	µg/ml	E.C.	%R.S.D.	E.C.	%R.S.D.	E.C.	%R.S.D.	E.C.	%R.S.D.
1.	90	90.46	0.6044	90.34	0.7061	90.06	0.1042	90.466	0.78188
2.	10	9.96	3.91	10.35	3.499	9.942	5.604	9.798	3.915
3.	2.5	2.486	5.68	2.53	8.32	2.596	4.163	2.594	7.23
4.	0.05	0.056	6.27	0.052	6.082	0.048	7.064	0.0516	8.83
Pure Drug	µg/ml	E.C.	%R.S.D.	E.C.	%R.S.D.	E.C.	%R.S.D.	E.C.	%R.S.D.
1.	90	90.36	1.24	90.94	1.24	90.98	0.907	90.808	1.4944
2.	10	9.88	2.35	10.01	1.01	10.07	2.837	10.094	2.8130
3.	2.5	2.516	1.27	2.49	1.53	2.494	2.7866	2.494	2.4814
4.	0.05	0.049	0.32	0.05	2.65	0.048	1.839	0.0496	3.05846

T.C. denotes theoretical concentration and E.C. denotes experimental concentration.

5. Stability: The stability of the drugs extracted from the plasma was subjected to short-term stability by keeping at -20 ºC for 30 days. The study indicated that the samples were stable where the percent ratios were within the acceptable limits of 90-110%. (Table 4)

Table 4: Storage stability data of valacyclovir in plasma at concentrations 90 and 10µg/ml

Matrix	Time (months)	Conc. Added (µg/ml)	Concentration Measured (µg/ml)			Mean	S.D.	%Dev
Plasma	Long stability		Assay 1	Assay 2	Assay 3			
	1	90	90.56	90.44	89.65	90.21	0.49	+0.23
		10	10.54	11.02	9.65	10.40	0.69	+4
	2	90	90.45	90.65	89.65	90.25	0.52	+0.17
		10	10.47	10.02	10.41	10.3	0.24	+3
	3	90	90.56	90.78	88.25	89.86	1.40	-0.255
		10	10.89	11.25	9.65	10.59	0.83	+5.9
	5	90	90.17	88.98	88.17	89.10	1.00	-1.099
		10	9.59	9.89	9.45	9.643	0.22	-3.57
	Freeze stability							
		90	91.25	90.56	89.59	90.46	0.83	+0.41
		10	10.65	11.14	10.59	10.79	0.30	+7.9

Matrix	Time (months)	Conc. Added (µg/ml)	Concentration Measured (µg/ml)			Mean	S.D.	%Dev
Drug in methanol	Long stability		Assay 1	Assay 2	Assay 3			
	1	90	90.14	90.43	90.57	90.38	0.21	+0.32
		10	10.51	10.14	10.23	10.29	0.19	+2.9
	2	90	90.54	90.05	90.58	90.39	0.29	+0.33
		10	10.51	10.11	10.58	10.4	0.25	+4
	3	90	90.23	90.15	88.89	89.75	0.75	-0.377
		10	10.48	10.47	10.12	10.35	0.20	+3.5
	5	90	90.57	90.43	90.12	90.37	0.23	+0.31
		10	10.04	9.54	9.15	9.576	0.44	-4.24
	Freeze stability							
		90	90.54	90.47	90.57	90.52	0.05	+0.477
		10	10.51	10.11	10.78	10.46	0.33	+4.6

6. Robustness: The robustness of the proposed method was found after altering the parameters deliberately: the mobile phase ratio variants: acetonitrile 14% and 16% for plasma and 10% and 12% in pure methanol, flow rate variants: 1.3 and 1.1 ml min-1for both. The retention time of the compound was evaluated, and the resolution had no significant changes when the parameters were changed. However, there was a change in the retention times with a change in flow rate, but this did not affect the peak symmetry. Each mean value was compared with the mean value obtained by the optimum conditions. A solution of 50 mg ml^{-1} of all the drugs extracted from the plasma was used for the study. The relative standard deviation (%RSD) was found to be within the limit. (Table 5 & 6)

Sample ID	Analytical Method	Valacyclovir Input (mg)	Valacyclovir Recovery (mg)	Valacyclovir Recovery (%)	Mean Recovery (%)	S.D.	%R.S.D.
1	Flow rate 1.1ml/min Mobile Phase: 12:44:44 Column: Phenomenix	10	9.26	92.6	96.025	2.564339	2.6704
2	Flow rate 1.2ml/min Mobile Phase: 10:45:45 Column: Phenomenix	10	9.56	95.6			
3	Flow rate 1.3ml/min Mobile Phase: 14:43:43 Column: Phenomenix	10	9.75	97.5			
4	Flow rate 1.2ml/min Mobile Phase: 12:44:44 Column: Phenomenix	10	9.84	98.4			

Table 6: Robustness for valacyclovir in plasma

Sample ID	Analytical Method	Valacyclovir Input (mg)	Valacyclovir Recovery (mg)	Valacyclovir Recovery (%)	Mean Recovery (%)	S.D.	%R.S.D.
1	Flow rate 1.1ml/min Mobile Phase: 12:44:44 Column: Phenomenix	10	9.26	92.6	96.025	2.564339	2.6704
2	Flow rate 1.2ml/min Mobile Phase: 10:45:45 Column: Phenomenix	10	9.56	95.6			
3	Flow rate 1.3ml/min Mobile Phase: 14:43:43 Column: Phenomenix	10	9.75	97.5			
4	Flow rate 1.2ml/min Mobile Phase: 12:44:44 Column: Phenomenix	10	9.84	98.4			

7. Assay of pharmaceutical formulations: The method developed was sensitive and specific for the quantitative determination of Valacyclovir and also was subjected to validation for different parameters; hence, it was applied for the estimation of drug in pharmaceutical formulations. Drug quantity equivalent to the labeled claim was weighed accurately and used for the assay. Each sample was analyzed in triplicate after extracting the drug as was mentioned above in the experimental section (2.3). The amounts of drugs were found to be within the range of 96-102%. None of the tablet excipients were found to interfere with the analyte peak as shown in Fig. 7.

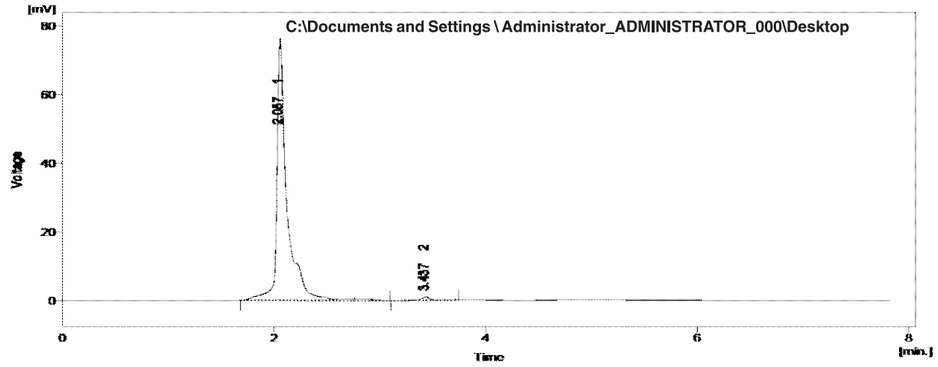

Figure 7: Chromatogram of Marketed Valacyclovir tablet 15mcg/ml

CONCLUSIONS

A simple, specific, selective and precise method was developed for the determination of anti-viral drugs valacyclovir. The mobile phase was easy to prepare with little or no variation with-out the involvement of buffers and was economical. The analysis time was found to be less than 4 min. The recovery from formulations and rat plasma were in good agreement and they suggested no interference in the estimation. Hence, this method can be easily and conveniently used for the routine quality control of the drugs in pharmaceutical dosage forms, can also be applied to clinical studies and pharmacokinetic study of the drug valacyclovir.

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NIOSOME: A NOVEL APPROACH FOR TARGETED DRUG DELIVERY

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ABSTRACT

The main goal of a site specific drug delivery system is not only to increase the selectivity but also to reduce the toxicity of the drug. Over the past several years, treatment of infectious diseases and immunisation has undergone a revolutionary shift. With the advancement in biotechnology and genetic engineering, not only a large number of disease-specific biologicals have been developed, but also emphasis has been laid on effective delivery of these biologicals. Different carriers like liposomes, niosomes, microspheres, resealed erythrocytes, dendrimers, aquasomes, transfersomes, ethosomes, phytosomes, nanoparticles etc. are used in novel drug delivery system. Vesicular systems are novel means of drug delivery that can enhance bioavailability of encapsulated drug and provide therapeutic activity in a controlled manner for a prolonged period of time. Niosomes are vesicles composed of non-ionic surfactants, which are biodegradable, relatively nontoxic, more stable and inexpensive, an alternative to liposomes. We review the current deepening and widening interest of niosomes in many scientific disciplines and, particularly its application in medicine. We also present an overview of the techniques of preparation of noisome, types of niosomes, characterisation and their applications.

KEYWORDS: Target cells, drug therapeutic index, lamellar, surfactants.

INTRODUCTION

The concept of drug targeting or site specific drug delivery was introduced for the first time by Paul Elrich in 1909, when he reported 'magic bullet' to deliver a drug to the desired site of action without affecting the non target organs or tissues (Juliano, 1980) by associating the drug with a pharmacologically 'inactive carrier' capable of conveying the drug selectivity towards the target cells. Target oriented drug delivery systems are the areas of major interest in modern pharmaceutical research. Selective drug delivery to the target tissues increases the therapeutic efficacy of the drug and reduces its undesirable effect to non target tissues. The main goal of a site specific drug delivery system is not only to increase the selectivity, but also to reduce the toxicity of the drug.

The concept of targeted drug delivery is designed for attempting to concentrate the drug in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. As a result, drug is localised on the targeted site. Hence, surrounding tissues are not affected by the drug. In addition, loss of drug does not happen due to localisation of drug, leading to maximum efficacy of the medication. Different carriers have been used for targeting of drug, such as immunoglobulin, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes and niosomes [1].

Niosomes are one of the best among these carriers. The self-assembly of non-ionic surfactants into vesicles was first reported in 1970s by researchers in the cosmetic industry. Niosomes (non-ionic surfactant vesicles) obtained on