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STUDIES ON EFFECT OF POLMER USING VALACYCLOVIR HYDROCHLORIDE

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ABSTRACT

Monolithics matrix tablet of Valacyclovir Hydrochloride where formulated as extended release tablet employing Ethyl cellulose polymer, Hydroxy propyl Methyl Cellulose polymer and extended release characterization of the formulated tablet was investigated. Sustained release tablet contain 500mg of Valacyclovir Hydrochloride were developed by changing concentration of drug polymers the 5:0.75, and 5:1.5 by direct compression. Formulation were based on the acceptable tablet properties in vitro and invivo drug release. The resulting formulations produced robust tablets with optimum hardness drug content, weight variation, disintegration and low friability. The result of in vitro and in vivo drug release studies indicated the formulations (Drug: Polymer=5:1.5) is the most successful of the study and exhibited constant and sustained release of Valacyclovir Hydrochloride release at the end of 12 hours compared with the reference standard. A decrease in the release of the drug was absorbed on increasing polymer ratio at a certain level. Further, the formulation F4 was subjected to exposure at room and accelerated condition to stability studies. There is no difference between storage temperature. And hence the formulation F4 was concluded as a better formulation.

KEYWORD: Valacyclovir Hydrochloride, Matrix tablet, Sustained release tablet, Ethyl cellulose and Hydroxypropyl methyl cellulose.

INTRODUCTION

In the recent years, sustained release drug delivery system are gaining more interest as these

systems deliver the drug continuously for prolonged period to maintain the steady stable blood level concentration, therefore providing reduction in the dosing frequency and increasing better patient compliance. These systems are designed mainly for the drugs which are required tobe taken frequently.

These sustained release delivery system are prepared using natural or synthetic or semi-synthetic polymers. They offer many advantages such as enhanced bioavailability, site-specific delivery, sustain release of drug over long period, retention of formulation in entire length of gastro intestinal tract, release of desired concentration of drug at targeted site and improved patient compliance due to reduction in frequent dosing.

Sustained release tablets are in a form of dosage where drug is administered to a patientat a given or calculated rate with the aim of maintaining a certain concentration of the administered drug over a specific period of time into the patient's system while reducing possibleside effects.

Principle behind sustained release system

Dissolution and diffusion controlled system have classically been of primary importance in oral delivery of medication because of their relative case of production and cost comparedwith other methods of sustained or controlled delivery.

The classification of such system is as follows:

- Diffusion controlled systems.
- Dissolution controlled systems.
- Dissolution and diffusion controlled systems.
- Osmotically controlled systems.
- Ion exchange systems.

MATERIALS AND METHODS

MATERIALS

Valacyclovir hydrochloride- gifted sample from Aurobindo Pharma Ltd., Visakha, HPMC K 100 M, Colorcon Asia pvt. Ltd., Goa., Ethyl cellulose (EC), Loba chemie pvt.Ltd., Mumbai., Dibasic calcium phosphate dihydrate, HI Media laboratories pvt. Ltd., Mumbai, Sodium aastarch glycolate, Loba chemie pvt.Ltd., Mumbai. Ethanol, Changshu Hongsheng Fine

chemicalco. Ltd., Changshu City. Magnesium stearate, Loba chemie pvt.Ltd., Mumbai, Talc, Loba chemie pvt.Ltd., Mumbai.

EQUIPMENTS

Beaker, Borosil, India. Calibrated pipettes, Borosil, India. Electronic balance, Shimadzu Bz-2204, Japan, Funnel, Borosil, India., Measuring cylinder, Borosil, India, Volumetric flask, Borosil, India. Friability apparatus, Veego scientific VFT-DV, India, Hardness apparatus, Monsanto, India, Dissolution apparatus, Veego scientific VDA-8DR, India, UV-spectrophotometer, Elico SL-159 spectrophotometer,Japan, Hot air oven, Chemi equipments, Bombay.

METHODS

PREPARATION OF SUSTAINED RELEASE MATRIX TABLET VALACYCLOVIR HYDROCHLORIDE

All the ingredients were separately passed through in a suitable sieve and then required quantity were mixed in a mortar. Then granules were prepared by wet granulation method. The granules were dried and again passed through suitable sieve to removed lumps and excessive fines. Finally the tablets were prepared by suitable tablet press. Before compressed the tablets,the granules were subjected to find out physicochemical parameter. Also the tablets were evaluated as per I.P & B.P.

Table 1: Formulation of Valacyclovir Hydrochloride 500mg (for 1 tablet).

INGREDIENTS	FORMULATION (mg/tablets)			
	F1	F2	F3	F4
Valacyclovir Hydrochloride	500	500	500	500
HPMC K100 M	75	150	_	_
Ethyl cellulose	_	_	75	150
Dibasic calcium phosphate dihydrate	104	29	104	29
Sodium starch glycolate	7	7	7	7
Ethanol	q/s	q/s	q/s	q/s
Magnesium stearate	7	7	7	7
Talc	7	7	7	7
Total weight	700	700	700	700

EVALUATION OF GRANULES

A) Angle of repose

The frictional force in the granules can bemeasured by the angle of repose. Angle of repose is calculated by fixed funnel method. In this method, funnel was fixed to stand so that the lower

tip of the funnel was 2.5cm above the surface, a graph paper was placed on flat surface. The blend was allowed to fall freely on the graph paper through the funnel, till the tip of the heap formed just touches the funnel. The radius of the heap was noted and from this angle of repose was determined. Angle of repose Θ can be calculated the equation as follows

$tan\ \Theta = h/r$

$\Theta = tan^{-1}h/r$

Where, h- Height of the heap in cm r- radius of the heap in cm

B) Bulk density

For the determination of bulk density a sample of about 10g was poured into a 50ml graduated cylinder. The cylinder was dropped at 2seconds interval into a hard wooden surface three times from a height of 2.5cm. The volume was recorded and the bulk density was calculated using the formula

Bulk density = Weight of granules/ Bulk volume of granules

C) Tapped density

A sample of about 10g was poured gently into a 50ml graduated cylinder. The cylinder was dropped at 2 seconds interval from a height of 2.5cm. The tapped density was calculated by measuring final volume after 100 taps on a wooden surface**.**

Tapped density = Weight of granules/ Tapped volume of granules

D) Carr's index or compressibility index (CI)

The packing ability of the powders was evaluated from the change in volume, which is due to rearrangement and packing occurring during tapping. It is expressed as carr's index or compressibility index (CI %) and is calculated as follows.

CI = (TD-BD)/TD * 100

Where, TD -Tapped density BD – Bulk density

E) Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

HR = TD/BD

Where, TD - Tapped density BD - Bulk density

A hausner's ratio <1.25 indicates good flow while >1.5 indicates poor flow.

EVALUATION OF SUSTAINED RELEASE TABLET OF VALACYCLOVIR HYDROCHLORIDE

A) Appearance

The tablets were visually observed for capping, chipping, and lamination.

B) Weight variation

To find out weight variation of 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was thencompared with average value to find the deviation in weight.

C) Hardness

The strength of a tablet to stand against applied pressure is known as hardness. It is also known as crushing strength. Randomly take 5-10 tablets from prepared batch and hardness should be determined by crushing the tablet by hardness tester (Monsanto apparatus) and then find out the average and standard deviation. The value of hardness was calculated in kg/cm^2.

D) Friability

Friability is the measure of tablet strength the test subjects a number of tablet to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at speed of 25rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre- weighed tablets was placed in Roche friabiltor which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. A loss of less than 1% in weight is generally considered acceptable. Percent friability (%F) was calculated as follows

$$\%F = (\text{Initial weight} - \text{Final weight})/\text{Initial weight}$$

E) Disintegration

Disintegration test was carried out at 37ºC±2ºC. Tablets were taken and introduced in each tube of disintegration apparatus, and the tablet rack of the disintegration apparatus was positioned into a 1 liter beaker containing 900ml of distilled water and the disc was not used for the study. The time taken for complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured.

F) Drug content (Assay)

The drug content in all the formulations were determined by triturating 10 tablets into fine powder weighed and transferred in the amount of powder equivalent to 60mg of Valacyclovir

Hydrochloride to a 100ml volumetric flask. Added 70ml of 0.1N HCl shaked by mechanical means and kept it for sonicator for 15min diluted with 0.1N HCl to a volume and filtered. Then pipette out 1ml of solution from this and transferred to the 100ml volumetric flask and makeup it using 0.1N HCl now the concentration of drug content is 6µg/ml in it. Then note its absorbance in UV spectrophotometer at 255nm.

G) *In-Vitro* dissolution studies

Preparation of buffer solution

Preparation of 0.1M Hydrochloric acid:

Dissolved 8.5ml of hydrochloric acid in 1000ml of distilled water

Preparation of phosphate buffer pH-6.8:

28.8g of disodium hydrogen phosphate and 11.45g of potassium dihydrogen phosphate were dissolved in 1 liter of water. Then the pH was adjusted to 6.8 with phosphoric acid or sodium hydroxide

Procedure

The *In-Vitro* dissolution studies of Valacyclovir Hydrochloride sustained release tablets were performed using USP dissolution apparatus type 1 (basket) at a rotational speed of 50rpm at 37ºC±0.5ºC. The dissolution media used were 900ml of 0.1N HCl for first 2 hours followed by pH 6.8 phosphate buffer solution for 12hours. Then withdraw 5ml of sample from the dissolutionmedium at regular interval (30min). The samples withdrawn were filtered through a 0.45µ membrane filtered and the drug content in each sample was analyzed after suitable dilution witha UV-spectrometer at 255nm.

H) Stability studies

In any rational drug design are evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection. Stabilityof a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until it's chemical or biological activity is not less than a predetermined level of labeled potency and it's physical characteristics have not changed appreciably or deleteriously**.**

Objective of stability studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance

or drug product varies with time under the influence of a variety of environmental factors such as temperature, Humidity and light, enabling recommended storage condition, re- test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time.

To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International conference on Harmonization (ICH) Guidelines titled stability testing of New Drug Substance and Products (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and the States of America.

ICH specifies the length of study and storage conditions

a) Long-Term Testing: 25^0 C ± 2^0 C at 60% RH ± 5% for 12 months

b) Accelerated Testing**:** 40^0 C ± 2^0 C at 75% RH ± 5% for 6 months.

In present study the selected formulation were exposure up to 3months stability studies at accelerated condition (40^0 C ± 2^0 C at 75% RH ± 5% RH) to find out the effect of aging on hardness, floating, characteristics, drug content and In-Vitro drug release.

Procedure

Stability studies were carried out at 25^0 C ± 2^0 C at 60% RH ± 5% for 1month. The samples were withdrawn and analyzed for its physical appearance, average weight, hardness, friability, disintegration, Drug content, In Vitro drug release after 3 month is completed.

RESULT AND DISCUSSION

EVALUATION OF GRANULES

The powder blends were evaluated for the micrometric properties such as angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio.

Table 2: Pre Compression parameter.

FORMULATION CODE	BULK DENSITY g/cm^3	TAPPED DENSITY g/cm^3	ANGLE OF REPOSE	CARR'S INDEX (%)	HAUSNER'S RATIO
F1	0.55±0.02	0.625±0.03	19.59±0.04	12±0.03	1.136±0.01
F2	0.526±0.04	0.55±0.03	18.96±0.02	4.36±0.02	1.045±0.03
F3	0.454±0.04	0.5±0.01	19.09±0.02	9.2±0.03	1.101±0.04
F4	0.357±0.01	0.384±0.04	17.72±0.03	7.03±0.03	1.075±0.02

DISCUSSION

The bulk density was found ranges between 0.357±0.01 and 0.55±0.02 g/cm^3, the tapped

density was found ranges between 0.384±0.04 and 0.625±0.03 g/cm^3, the Carr's index was foundranges between 4.36±0.02 and 9.2±0.03 % and the Hausner's ratio was found ranges between 1.045±0.03 and 1.136±0.01. The angle of repose was found a range between 17.72±0.03 and 19.59±0.02 which showsan excellent flow property.

EVALUATION OF SUSTAINED RELEASE TABLET OF VALACYCLOVIR HYDROCHLORID

A) Appearance

The tablets were observed visually and did not show any defect such as capping, chippingand lamination.

B) Other parameters

Table 3: Post compression parameter.

Formulation code	Weight variation (%Deviation)	Hardness Kg/cm^2	Friability (%)	Disintegration (at 30min)
F1	0.251±0.04	11.21±0.02	0.444±0.01	Not disintegrate
F2	0.831±0.03	10.75±0.02	0.073±0.03	Not disintegrate
F3	0.441±0.01	11.5±0.03	0.215±0.04	Not disintegrate
F4	1.258±0.02	11.4±0.03	0.071±0.03	Not disintegrate

DISCUSSION

Weight variation

20 tablets of each marketed formulation were selected for weight variation test. The accepted percentage deviation was ±5.0 for 250mg or more weight tablets. The results showedthe weight variation range from 0.251±0.04 to 1.258±0.02 mg.

Hardness

The hardness of the 10 tablets of each formulation was measured. The result of hardness of all the tablets are shown at the above given table 9.2. The hardness of all the formulations was found to be in ranges of 10.75±0.02 and 11.5±0.03 Kg/cm^2. It indicate all tablets in the formulations have good mechanical strength.

Percentage friability

Friability test was done by Roches friabilator. The maximum weight loss should not more than 1%. The result of weight loss of the tablets showed that all the formulations were expressed in the table. It was found to be ranges of 0.071±0.03 and 0.444±0.01%.This indicate the good handling property of the tablet.

Disintegration

All tablet formulation doesn't disintegrate at 30 min at 37ºC in both water and HCl. Hence it passes disintegration test. It produces an sustained release action.

C) Analytical method

1. Drug content (Assay)

The percentage purity of 4 formulations was found to be an range between 91.68±0.01 and 99.18±0.03 % which is compiled in the pharmacopoeia.

Table 4: Percentage purity of the formulation by UV Spectroscopy.

S.NO	FORMULATION CODE	PERCENTAGE PURITY(%)
1.	F1	94.664±0.02
2.	F2	91.68±0.01
3.	F3	96.66±0.02
4.	F4	99.18±0.03

DISCUSSION

All the formulations have an percentage purity within the limit as per USP.

2. In-Vitro Dissoltion studies

Preparation of standard curve of Valacyclovir Hydrochloride in 0.1 N hydrochloric acidbuffer

Various concentration of Valacyclovir Hydrochloride in 0.1N hydrochloric acid was absorbed in UV at 255nm. The curve of absorbance versus concentration for Valacyclovir hydrochloride was found in linear from the concentration range 2-10µg/ml shown in table 5 and figure 1

Table 5: Absorbance of Valacyclovir Hydrochloride in 0.1 N HCl.

S.NO.	CONCENTRATION (µglml)	ABSORBANCE 255nm
1.	0	0
2.	2	0.0657±0.02
3.	4	0.1103±0.01
4.	6	0.1503±0.02
5.	8	0.199±0.030
6.	10	0.2451±0.04

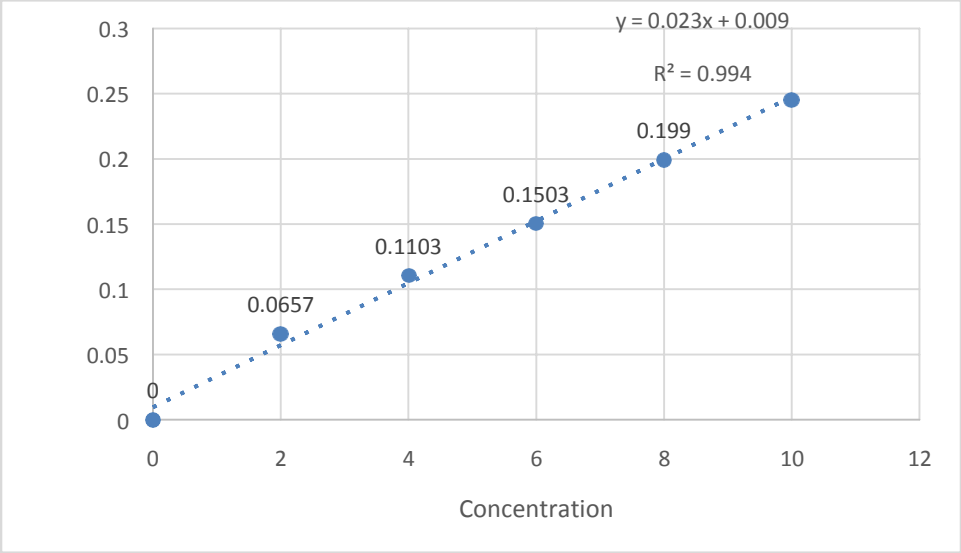

Figure 1: Standard curve of Valacyclovir Hydrochloride in 0.1N HCl.

Table 6: Standard curve value.

S.NO	PARAMETERS	VALUES
1.	Slope(m)	0.023
2.	Intercept(c)	0.009

Preparation of standard curve Valacyclovir Hydrochloride in pH 6.8 phosphate buffer:

The various concentration of Valacyclovir Hydrochloride in pH6.8 phosphate buffer was absorbed 252nm. The curve of absorbance versus concentration of Valacyclovir Hydrochloride was found in linear concentration range 2-10µg/ml shown in table 7 and figure 2.

Table 7: Absorbance of Valacyclovir Hydrochloride in pH 6.8 Phosphate buffer.

S.NO.	CONCENTRATION (µg/ml)	ABSORBANCE (252nm)
1.	0	0
2.	2	0.065±0.03
3.	4	0.122±0.03
4.	6	0.202±0.01
5.	8	0.241±0.04
6.	10	0.271±0.02

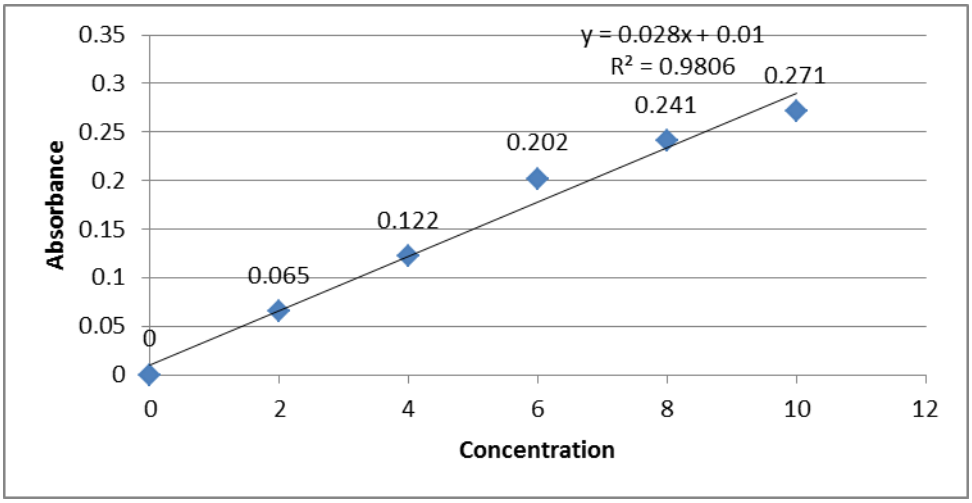

Figure 2: Standard curve of Valacyclovir Hydrochloride in pH 6.8 Phosphate buffer.

Table 8: Standard curve value.

SI.NO	PARAMETERS	VALUES
1.	Slope (m)	0.028
2.	Intercept (c)	0.01

In-Vitro drug release of Valacyclovir Hydrochloride sustained release tablets for all the formulations are studied in 0.1N hydrochloric acid dissolution media for first 2hours followed bypH 6.8 phosphate buffer solution for remaining 10 hours and values shown in the given below table 9 and figure 3.

Table 9: Percentage of cumulative drug release of Valacyclovir Hydrochloride in 0.1N HCl and pH 6.8Phosphate buffer dissolution medium.

DISSOLUTION MEDIUM	TIME INTERVAL (Hours)	% CUMULATIVE DRUG RELEASE			
		F1	F2	F3	F4
In 0.1 N Hydrochloricacid	0	0	0	0	0
	1	30.9±0.02	21.4±0.03	25.3±0.02	16.5±0.02
	2	70.2±0.01	49.9±0.02	52.7±0.02	40.1±0.01
In pH 6.8 Phosphate buffer	3	79.8±0.02	62.9±0.01	72.8±0.02	53.1±0.02
	4	86.6±0.04	71.8±0.03	81.3±0.03	60.4±0.04
	5	91.4±0.02	80.9±0.01	88.5±0.02	64.6±0.01
	6	96.3±0.02	85.7±0.01	92.5±0.04	69.5±0.03
	7	-	89.8±0.02	95.9±0.03	76.8±0.03
	8	-	92.9±0.01	98.8±0.02	80.9±0.04
	9	-	94.7±0.04	-	84.8±0.01
	10	-	97.4±0.01	-	88.3±0.03
	11	-	-	-	93.6±0.04
	12	-	-	-	99.1±0.02

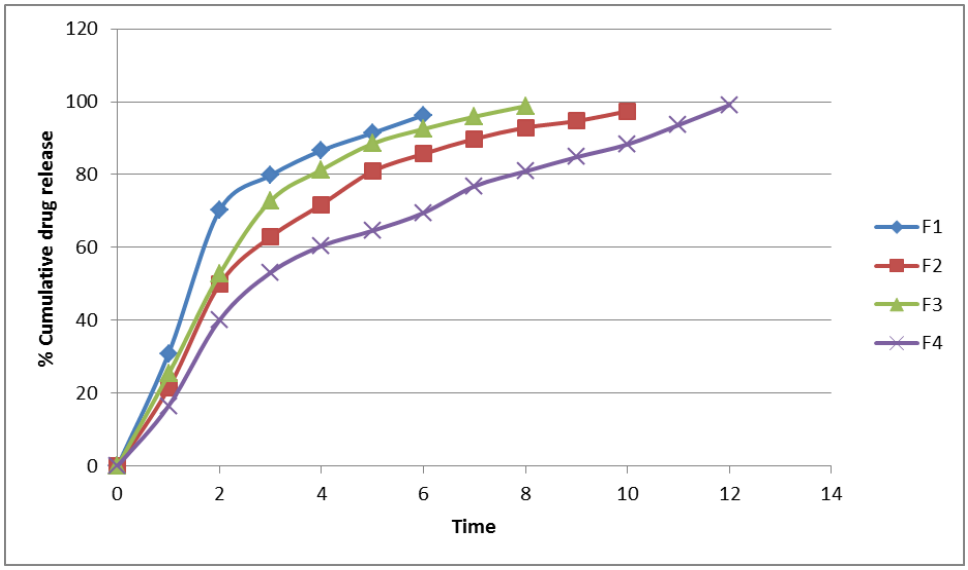

Figure 3: Time Vs % Cumulative drug release.

3. Stability studies

The stability study was carried out for optimized formulation (F4) by strip packing and was stored at 25±2ºC/60%±5% RH for a period of one month. The tablets were evaluated for various parameters like physical appearance, average weight, hardness, friability, disintegration, in-vitro dispersion, dissolution and drug content at one month interval and its stability was shown in given below table10

Table 10: Stability studies of optimized formulation (F4).

Characteristics	Initials	1 Month	2 Month	3 Month
Weight variation (% deviation)	1.258±0.02	1.246±0.02	1.244±0.01	1.238±0.03
Hardness (Kg/cm^2)	11.4±0.01	11.2±0.01	11.0±0.02	10.9±0.02
Friability (%)	0.071±0.03	0.072±0.02	0.074±0.02	0.076±0.01
Disintegration	Not disintegrate	Not disintegrate	Not disintegrate	Not disintegrate
Drug content (%)	99.18±0.03	99.16±0.04	99.15±0.02	99.11±0.03
In vitro drug release at 12 hours.	99.1±0.02	98.98±0.03	98.6±0.01	98.39±0.02

CONCLUSION

In the present dissertation work an attempt was made to designed and developed Valacyclovir Hydrochloride sustained release matrix tablets using HPMC K100M and Ethyl cellulose as release retarding polymers. Valacyclovir Hydrochloride was widely used as anti-viral drug; therefore have been selected and prepared sustained release dosage forms for prolong released.

An ideal matrix formulation prepared with different polymers and diluents concentration should released its content in a sustained manner at a reasonable length of time and preferably with zero order kinetics.

The active pharmaceutical ingredient Valacyclovir Hydrochloride was evaluated for its physicochemical characteristics, analytical profile study. The powder blend was prepared by mixing all ingredients in mortar. The prepared powder blend was evaluated for angle of repose, bulk density, tapped density and Carr's index. The results obtained were found to be satisfactory and within the specified limits.

Valacyclovir Hydrochloride sustained release tablet was prepared by using wet granulation method and an active medicament, polymer and other additives concentrations were optimized by various trials of tablets. The optimization procedure aided in the stabilization of the formula. After compression the following parameters of thickness, hardness, weight variation, friability, content uniformity, disintegration and In-Vitro release studies were evaluated.

Result of the present study demonstrated that both the hydrophobic and hydrophilic polymers could be successfully employed for formulating sustained release matrix tablets of Valacyclovir Hydrochloride. The investigated sustained release matrix tablet was capable of maintaining constant plasma concentration upto 6hrs. This can be expected to reduced the frequency of administration and decreased the dose dependent side effect. The efficacy and safety of Valacyclovir Hydrochloride tablet dosage form were expected to offer optimum therapeutic efficacy and improved patient compliance.

From the prepared four formulation (F1,F2,F3 and F4) the formulation F1 drug released up to 6 hours, F2 drug released up to 10 hours, formulation F3 drug released up to 8 hours and formulation F12 drug released up to 6 hours. The formulation F4 was selected according to drug release profile.

According to 1 month stability study the formulation (F4) showed that there was no significant change in the physicochemical parameter and *In-Vitro* drug release studies. So the formulation F4 was concluded the best formulation among other formulations.

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