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Formulation and Evaluation of Valacyclovir hydrochloride Mouth Dissolving Film

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ABSTRACT

Valacyclovir hydrochloride is widely used for the treatment on Herpes virus, illness caused by Herpes virus such as Genital herpes, Cold sores, Chingles and Chicken pox. The present study is deals with formulation, optimization, evaluation of Valcyclovir HCL mouth dissolving films. Genital herpes, Cold sores, Chingles and Chicken pox are the conditions where instance effect of drug is required. Valacyclovir hydrochloride is one of the drug which is used in the treatment of above three disease conditions. The mouth dissolving films was prepared by using solvent casting method. The concentration of propylene glycol, sodium lauryl sulphate (SLS) were kept constant in all formulations (F1-F4) and varying concentration of hydroxy propyl methyl cellulose(HPMC) and methyl cellulose. All the formulations were evaluated for surface pH, weight uniformity, folding endurance, drug content, disintegration time, in-vitro dissolution studies. The formulation 'F3' was found to be optimized formulation. It shows results for all evaluation parameters such as weight variation 34.70±0.7mg, surface pH 6.75±0.60, folding endurance > 100, drug content 95.25±1.10%, disintegration time 30±0.50 sec, and in-vitro dissolution study 81.35±1.30 % at the end of 5 min.

keywords: Fast dissolving film, Valacyclovir hydrochloride, Solvent casting, Hydroxyl propyl methyl cellulose, Chicken pox, Genital herpes.

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INTRODUCTION

The oral route is most popular route for the administration of various drugs. The ease of administration leads to high levels of patient compliance. Approximately one-third part of the population, primarily the geriatric andpaediatricpatients has a problem of swallowing it leads to cause poor patient compliance with oral tablets/capsules drug therapy which reduces the therapy effectiveness. To overcome such difficulties the sublingual films are one of best drug delivery system[1-3,] The mouth dissolving films contain active drug material incorporated into polymeric film. The various film forming polymers are available in the market which havewide range of compatibility with most of drug[2]. The fast dissolving films contain such film forming polymer which can be disintegrate rapidly in mouth due to presence of saliva. By giving the drug from oral route it is converted by esterases to the active drug acyclovir as well as the amino acid valine via hepatic first pass metabolism[3].

Criteria for Fast Dissolving Film[4]

Fast dissolving film should:-

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Exhibit low sensitivity to environmental conditions such as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging equipment at low cost.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.

MATERIALS AND METHOD

Materials

Valacyclovir hydrochloride was received as a gift sample from Millen Laboratories Pvt. Ltd. Nashik, HPMC- E5 was obtained from Space Lab. Nashik, all other chemicals used were obtained from commercial sources and were of analytical grade.

Method

Films were prepared by using solvent casting method[2,4-13]. Polymer was weighed and dissolved in alcohol (solution A). In another beaker the drug solution was prepared (solution B) and mix both this solution (A and B) with the help of magnetic stirrer. The glycerine, vanillin and SLS were added to above solution and stir continuously for 30 minutes. After stirring kept this solution in

sonicator for complete removal of air bubbles and then transfer the solution in petridish and allowed to dry at room temperature for 24 hours. After drying, these films were removed from the petridish and cut into definite shapes and size. For furtherevaluation films are packed in aluminium foil and placed in desiccators[2,5-13].

Table 1 Composition of Valacyclovir hydrochloride fast dissolving film:

Sr. no.	Ingredients(mg)	F1	F2	F3	F4
1	Valacyclovir hydrochloride	10	10	10	10
2	HPMC	1000	1500	-	-
3	Methyl cellulose	-	-	1000	1500
4	Propylene glycol	10%	10%	10%	10%
5	SLS	3%	3%	3%	3%
6	Vanilla	QS	QS	QS	QS
7	Colour	QS	QS	QS	QS
8	Water	QS	QS	QS	QS

EVALUATION OF VALACYCLOVIR HYDROCHLORIDE FAST DISSOLVING FILMS:

Appearance, Shape and Thickness:

The formulated films of Valacyclovir hydrochloride were checked for their appearance, shape and thickness. The thickness of randomly selected 5 test films was determined at five different places using a micrometer and mean value was calculated[2-13]]

Weight variation:

Weight variation test was performed by taking weight of films of every formulation individually and then weight was calculated[2,4-7,9-13].

Surface pH:

The surface pH of films was determined by placing film in petridish and moistened with few drops of distilled water and allowed to moisten for 1 hrs. After that bring aelectrode of pH meter in contact with surface of film and pH were noted[2,4-7,9-13].

Folding endurance:

The folding endurance is expressed as the number of folds (number of times the film is folded at the same place, either to break the specimen or to develop visible cracks). This also gives an indication of brittleness. The folding endurance of the strips can be determined by repeatedly folding one film at the same place till it broke[4-13].

Drug content:

The films (area 2x2 cm2) was placed in beaker and to this add sufficient volume of phosphate buffer pH 6.8 and dissolved the film with the help of magnetic stirrer. Filter this solution and transferred into 100ml volumetric flask make up final volume (100ml) with phosphate buffer pH

6.8 solution. The absorbance of solution was measured at _ max 237 nm using UV spectrophotometer (LABINDIA 3000+ UV-VIS spectrophotometer). The experiment was performed in triplicate[2,5-13].

Disintegration time:

The disintegration time limt for is of 30 sec or less for orally disintegration tablet. In vitro disintegration time was determined by placing the film (area 2x2 cm2) in beaker containing 10 ml of phosphate buffer pH 6.8 and swirling at interval of 5 sec. The time at which films start to disintegrate considered as disintegration time[2,5-13]

Preparation of calibration curve of Valacyclovir hydrochloride:

Weigh quantity of Valacyclovir hydrochloride (100mg) place in 100 ml of standard volumetric flask and make up the volume with simulated saliva pH 6.8. The stock solution obtained is 1000 µg/ml solution. Aliquots of 0.5, 1, 1.5, 2,2.5 and 3 ml of stock solution pipette out into 100 ml standard volumetric flasks and final volume adjust up to 100 ml with simulated saliva pH6.8 to give the concentration of 5, 10, 15, 20, 25 and 30µg/ml. The absorbance measure at 238 nm in UV spectrophotometer against reagent blank with simulated saliva pH 6.8 (Table 3and Figure 1)[2,5-12].

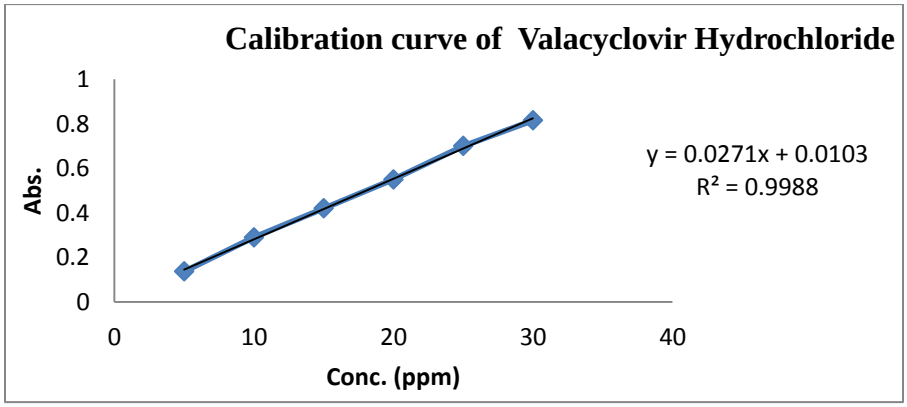


Figure 1. Standard calibration curve of Valacyclovir hydrochloride.

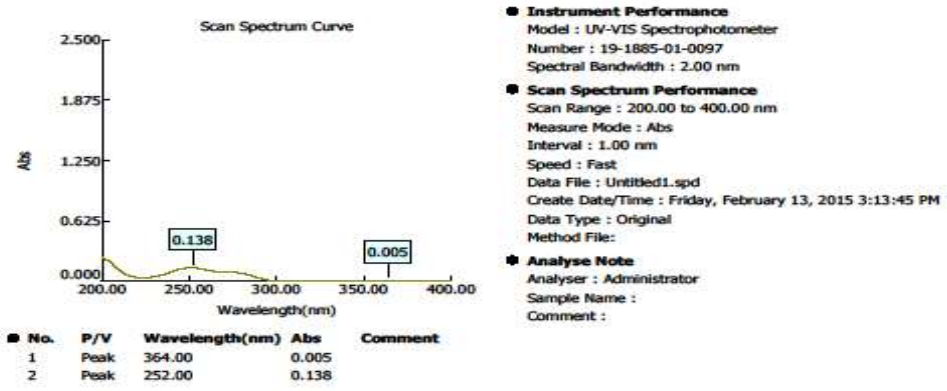


Figure 2. UV spectrum of Valacyclovir hydrochloride.

In-vitro dissolution study:

In vitro dissolution study can be perform using a paddle or basket type apparatus describe in pharmacopoeia. The in-vitro drug release study was carried out using USP dissolution test apparatus (USP type II) at temperature 37±0.5ºc and 50 rpm. The phosphate buffer pH 6.8 was used as the medium. During study 5ml of test sample was withdraw at 15sec. intervals and the absorbance of sample taken at 252nm with the help of UV spectrophotometer (LABINDIA 3000+ UV-VIS spectrophotometer). Thevalues were transformed into concentration using standard calibration curve. The results are shown in table no. 4[2-13].

RESULT AND DISCUSSION

Valacyclovir hydrochloride mouth dissolving films were prepared and evaluatedfor appearance, size, shape, thickness, surface pH, weight variation, folding endurance, drug content, disintegration and dissolution study. All the films were prepared by different polymer concentration were found to be flexible, non sticky, smooth, transparent and homogeneous.

Thickness was varies between 0.105±0.005 mm to 0.116±0.006 mm. the marginal difference in the thickness was observed among each group indicated that the more amount of polymer. The formulation 'F3' shows thickness 0.0.116±0.006mm, there was no significant difference in S.D (table 6).

The weight of films (formulation F1-F4) was found to bein range of 32.20±0.mg to 34.70±0.7mg, the weight of formulation 'F3' was 34.70±0.7 mg. The individual weight of sample of each type of formulation was determined and the average weight was calculated. It was observed that weight of the entire film sample in each formulation was uniform. The S.D. value was not significantly varies and meet the criteria for the weight variation as shown in table no. 2. and table 5.

Surface pH was varies in the range of 6.10±0.5 to 6.75±0.60 which is very close to neutral pH, which indicated that film may have less potential to irritate the sublingual mucosa thereby they are comfortable. The formulation 'F3' was shows the pH 6.75±0.60 since this value was nearest to the pH of saliva i.e. 6.8.

Folding endurance for all the formulations was found to be more than 100 folds. It might be due to the formation of strong hydrogen bond between polymer and plasticizer there by imparting to flexibility to withstand rupture.

All the formulation was evaluated for the drug content. The result obtained was shown in table no. 2 and figure 1 & 2. The formulation 'F3' shows maximum amount of drug 95.25±1.10 it indicated good content uniformity.

Disintegration time of each formulation was determined. It was varies in range between 28±0.30 sec. to 30.±0.50 sec. The disintegration time was decrease and increase because of concentration or type of polymer. The disintegration time for the formulation 'F3' was found to be 30.±0.50 sec.

The in-vitro drug release study was carried out using USP dissolution test apparatus type-II. The rate and extent of drug release was faster, this was because of water soluble polymers that increase wettability and penetration of water into the film matrices and hence increase diffusion of the drug. The results obtained were shown in table no. 4 and fig. no. 3. The formulation 'F3' shows 81.35% drug release at the end of 5 minutes.

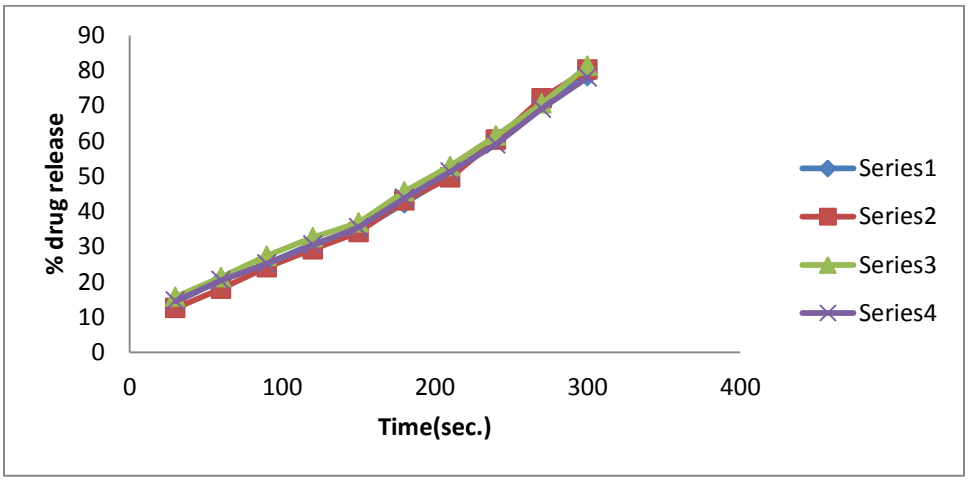
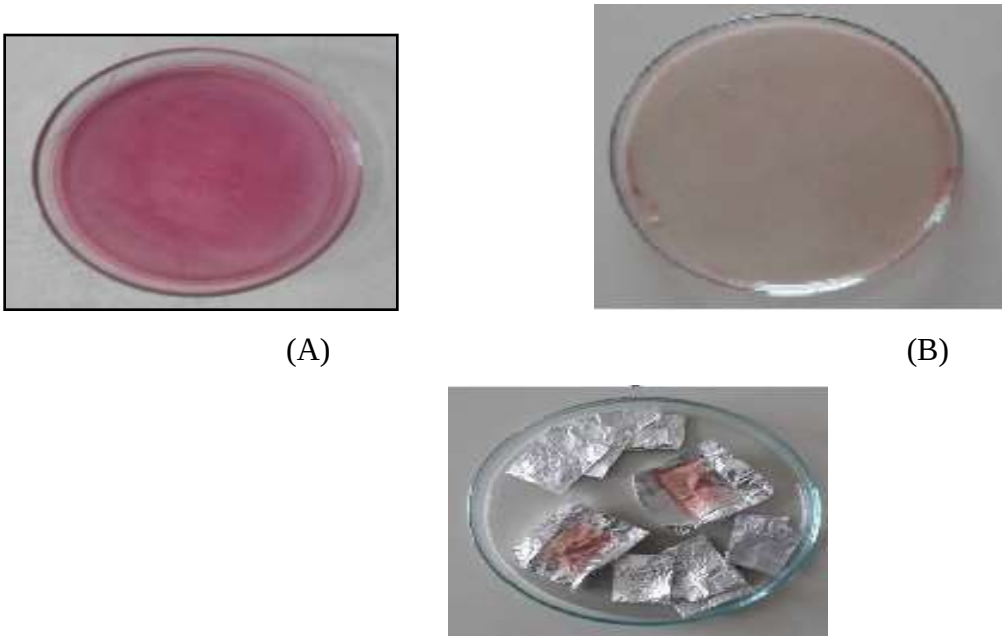


Figure 3. % Drug release of Valacyclovir hydrochloride formulation F1-F4



(A) (B)

(C)

Figure 4: A- film of HPMC and colour, **fig: B**- Film of methyl cellulose containing Valacyclovir hydrochloride, **fig:C**- Packaging of film.

Table : 2 Result of evaluation of Valacyclovir hydrochloride mouth dissolving film.

Parameter	Formulations			
	F1	F2	F3	F4
Thickness(mm)	0.105±0.005	0.114±0.005	0.116±0.006	0.110±0.002
Mean weight(mg)	32.20±0.2	34.05±0.5	34.72±0.6	32.58±0.5
Drug content(%)	94.20±1.20	88.36±0.68	95.25±1.10	93.65±1.05
Disintegration time(sec)	29±0.50	28±1.20	30±0.50	28±0.30
Surface pH	6.10±0.5	6.35±0.25	6.16±.30	6.75±0.60
Folding endurance	>100	>100	>100	>100

Table: 3 Absorbance –concentration data for standard curve of Valacyclovir hydrochloride.

Sr. no.	Concentration (µg/ml)	Absorbance			
		I	II	III	Average
1.	0	0.000	0.000	0.000	0.000
2.	5	0.137	0.138	0.137	0.137
3.	10	0.291	0.290	0.289	0.290
4.	15	0.418	0.420	0.422	0.420
5.	20	0.551	0.549	0.550	0.550
6.	25	0.700	0.768	0.772	0.700
7.	30	0.813	0.815	0.817	0.815

Table 4: In-vitro drug release study of Valacyclovir hydrochloride fast dissolving films.

Sr. no.	Method	Time(sec.)	%Drug release			
			F1	F2	F3	F4
1.		0	0	0	0	0
2.		30	14.25	12.60	15.75	14.60
3.		60	20.55	18.10	21.35	20.45
4.		90	25.20	24.16	27.44	25.15
5.	Solvent casting	120	30.85	29.24	32.64	30.50
6.		150	34.54	34.10	36.86	35.42
7.		180	42.35	43.10	45.65	43.75
8.		210	50.15	49.65	52.85	51.24
9.		240	60.40	60.35	61.55	59.10
10.		270	71.84	72.15	70.65	69.21
11.		300	78.36	80.25	81.35	78.10

Table. 5: Average weight of Valacyclovir hydrochloride fast dissolving film:

Sr. no.	F1(mg)	F2(mg)	F3(mg)	F4(mg)
1.	32.10	34.30	34.55	32.45
2.	32.50	33.90	34.90	32.55
3.	32.00	34.00	34.80	32.60
4.	32.20	34.20	34.65	32.75
Average	**32.2±0.2**	**34.1±0.3**	**34.72±0.72**	**32.25±0.5**

Table. 6: Average thickness of Valacyclovir hydrochloride fast dissolving film:

Sr. no.	F1(mm)	F2(mm)	F3(mm)	F4(mm)
1.	103	117	117	109
2.	108	114	115	111
3.	104	114	116	110
Average	**105±0.005**	**114±0.005**	**116±0.006**	**110±0.002**

CONCLUSION

All the prepared films was evaluated for different parameters and the formulations were shows satisfactory results. The formulation 'F3' shows comparatively good results for all evaluation parameters. Hence we conclude that the formulation 'F3' is optimized formulation.

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