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Effect of Formulation Variables on the Swelling Index of Acyclovir Sustained Release Tablets Using Xanthan Gum and Sodium Alginate

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Abstract

The swelling index characterizes the rate at which a tablet will dissolute and is also an indicative of the mechanism. The present study focuses on studying the effect of swelling capacity of Acyclovir Sustained release tablets such that for all formulations it increases as increase the concentration of gum in each formulation. The swelling index of all formulation increases as increase the concentration of gum in each formulation. Swelling of matrix tablets increases with respect to time because weight gain by tablets was increased proportionally with rate hydration up to 4hrs and matrix appeared swollen almost from the beginning and a viscous gel mass was created after contact with water later on swelling were decreases due to dissolution of outermost gelled layer of tablets. Swelling index of tablets prepared from ACL3 resulted as better swelling behavior with respect to concentration. It has observed that drug release decreases with increasing concentration of gum and swelling index. The reason attributed to this fact is formation of thick gel layer by matrices around tablets that delays diffusion and release drug. It has observed that swelling index of matrix tablets containing only one natural polymer was less this may attributed to the lower water uptake and less hydrophilicity.

Keywords: Sustained release, hydration, acyclovir, hydrophilicity**.**

Introduction

Acyclovir is an anti-retro-viral drug active in vitro against Herpes simplex (HSV) types I and II and Varicella zoster virus (VZV). Acyclovir needs to be phosphorylated to the active compound, aciclovir triphosphate, in order to become active against the virus. The conversion is confined to normal cells and in addition cellular DNA polymerase is not very sensitive to the active compound[1,2].

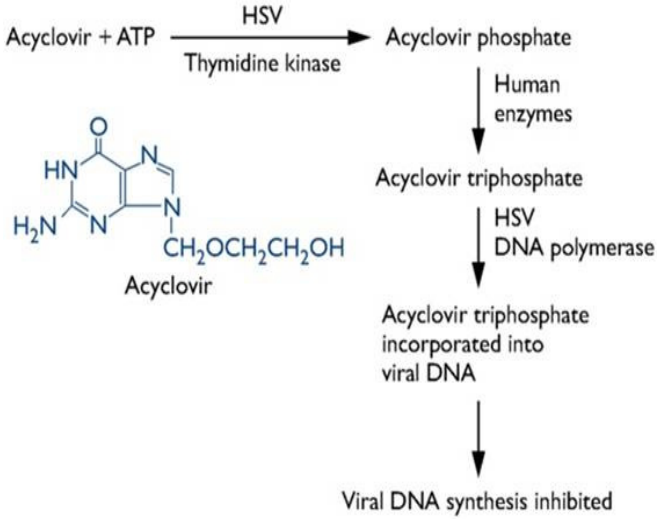

Figure-1
Mechanism of action of Acyclovir

Sustained release SR tablets dosage forms are preferred for drugs with low oral bioavailability. Pure acyclovir is a drug candidate with low oral bioavailability and a desired pharmacokinetic profile for Sustained release drug release[3]. After oral doses of 200 mg taken four to five times daily or 400 mg taken two to three times daily, the peak plasma concentration is about 2 micromol/L (0.49 mcg/mL) unstable plasma half life depending upon absorption is 2.9 to 3.3 hrs.

Sustained release drug delivery bestows upon[3]: i. Uniform drug delivery at the site of action owing to lower fluctuations in the dissolution and bioavailability during the therapeutic regime of the drug. ii. The fact that time dependent release and drug-excipient ratios would be optimized, bioavailability determination becomes more accurate. iii. The area under the curve and the pharmacokinetic data produced now would be in accordance to dose optimization and drug excipient ratios.

The present study studies the effect of swelling profile on the drug release mechanism in a Sustained release drug delivery system.

Methodology

Materials: Nishka Labs, Hyderabad, provided the pure drug Acyclovir analytical grade along with excipients like xanthan gum, microcrystalline cellulose (MCC), sodium alginate, talc and hydroxy-poly-methyl-cellulose (HPMC) K15. Mannitol, sodium chloride and potassium dihydrogen ortho phosphate were bought from SD Fine Labs Mumbai. Xanthan gum,

sodium alginate and MCC are three polymers whose ratios were optimized in the current study for preparation of Acyclovir Sustained release formulation.

Preformulation: Organoleptic Characteristics: The color, odor, and taste of the drug were characterized and recorded using descriptive terminology; the results were shown in the table 1.

Table-1
Organoleptic Characteristics of Acyclovir

Properties	Result
Odour	Odourless
Colour	White
Form	Crystalline

Melting point: The melting point of the pure drug acyclovir was reported in table 2.

Table-2
Melting point of Acyclovir

Sample	Reported	Observed
Acyclovir	255^0C	255.9^0C

Solubility analysis: The solubility was performed visually by dissolving in suitable solvents and water. The available literature on solubility profile of acyclovir indicated that the drug is very soluble in methanol, DMSO, dioxane and ethanol[4,5]. Practically insoluble in water. Acyclovir was found to be soluble in methanol, ethanol and DMSO. The study was carried out to select suitable dissolution medium for *in-vitro* release studies.

Table-3
Observations for Standard graph of Acyclovir in pH 6.8 at 256 nm

Concentration (µg/ml)	Absorbance (236nm) in pH 6.8
2	0.185
4	0.312
6	0.403
8	0.531
10	0.604
12	0.705
14	0.769
16	0.874
18	0.978
20	1.18

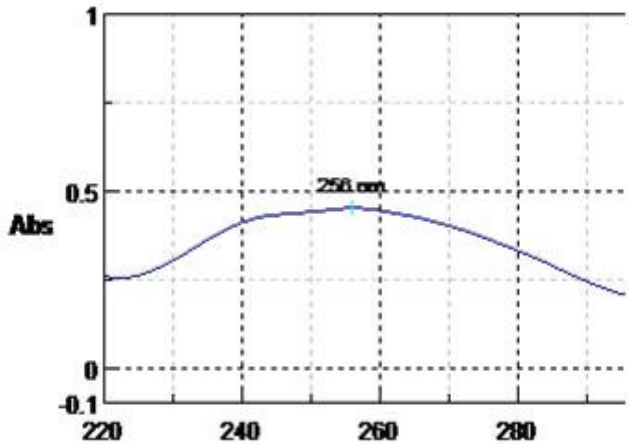

Figure-2
λmax of Acyclovir in pH 6.8 at 256 nm

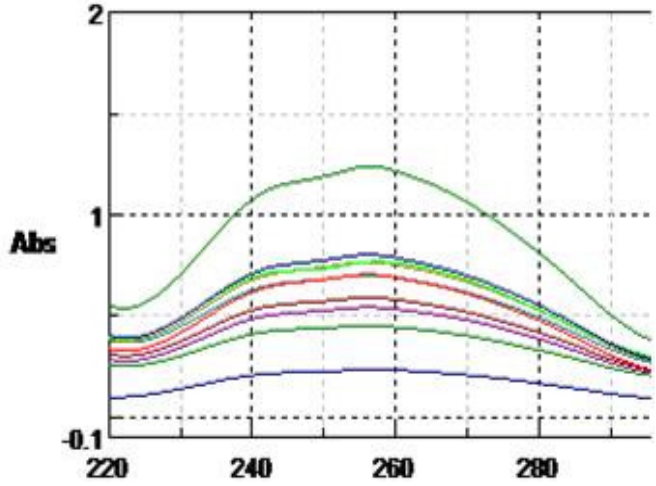

Figure-3
Overlay Spectrums of Acyclovir in pH 6.8 at 256 nm

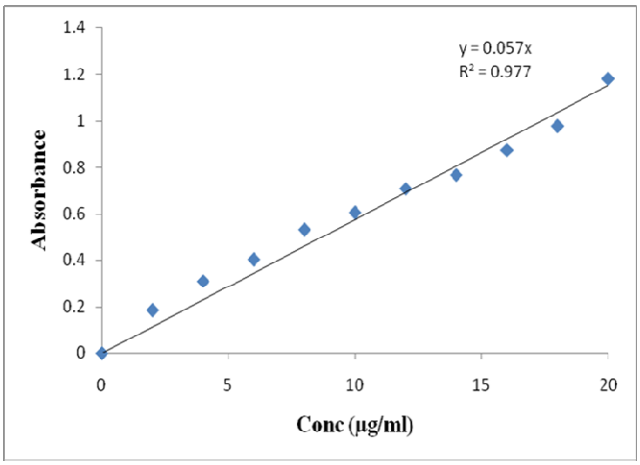

Figure-4
Calibration curve of Acyclovir in pH 6.8 at 256 nm

FT-IR spectral analysis (Drug excipient Compatibility study): The development of a successful formulation depends only on suitable selection of excipients. The physicochemical compatibility of the drugs and the polymer was obtained by FTIR studies.

Table-4
Wave number of different functional groups of Acyclovir

S.No	Formulation	Wave number
1	Acyclovir	3949.5, 3847.29, 3791.37, 3669.87, 3563.81, 3444.24, 3347.82, 3251.4, 2856.06, 2763.49, 2350.8, 1714.41, 1594.84, 1482.99, 1421.28, 1307.5, 1143.58, 1083.8, 869.73, 779.1, 682.67, 680.469, 636.11

The FTIR Spectrum of Pure acyclovir showed peaks at 3563.81 cm-1 (O-H stretching), 1608.63 cm-1 (O-H deformation), 3444.24 cm-1 (10 N-H stretching), 2927.94 cm-1 (aliphatic C-H stretching anti symmetric), 2856.06 cm-1 (aliphatic C-H stretching symmetric), 1482.99 cm-1 (aliphatic C-H deformation), 1714.41 cm-1 (C=O stretching) and 1143.8 cm-1 (C-O stretching). Therefore, there was no alteration and no interaction was observed between excipients and drug in combination. All the characteristic peaks of acyclovir were present in combination, thus indicating compatibility between drug and excipients and finally confirm that there was no chemical modification of drug has been taken place.

DSC studies: DSC thermo gram of acyclovir is presented in figure 6. In case of Acyclovir two endothermic peaks were observed one at 197^{0}C, which corresponds to melting process and the other at 236^{0}C due to thermal decomposition. Thus from IR spectra studies and DSC thermo grams we can draw a conclusion that the drug remains in its normal form without undergoing any interaction with the polymers.

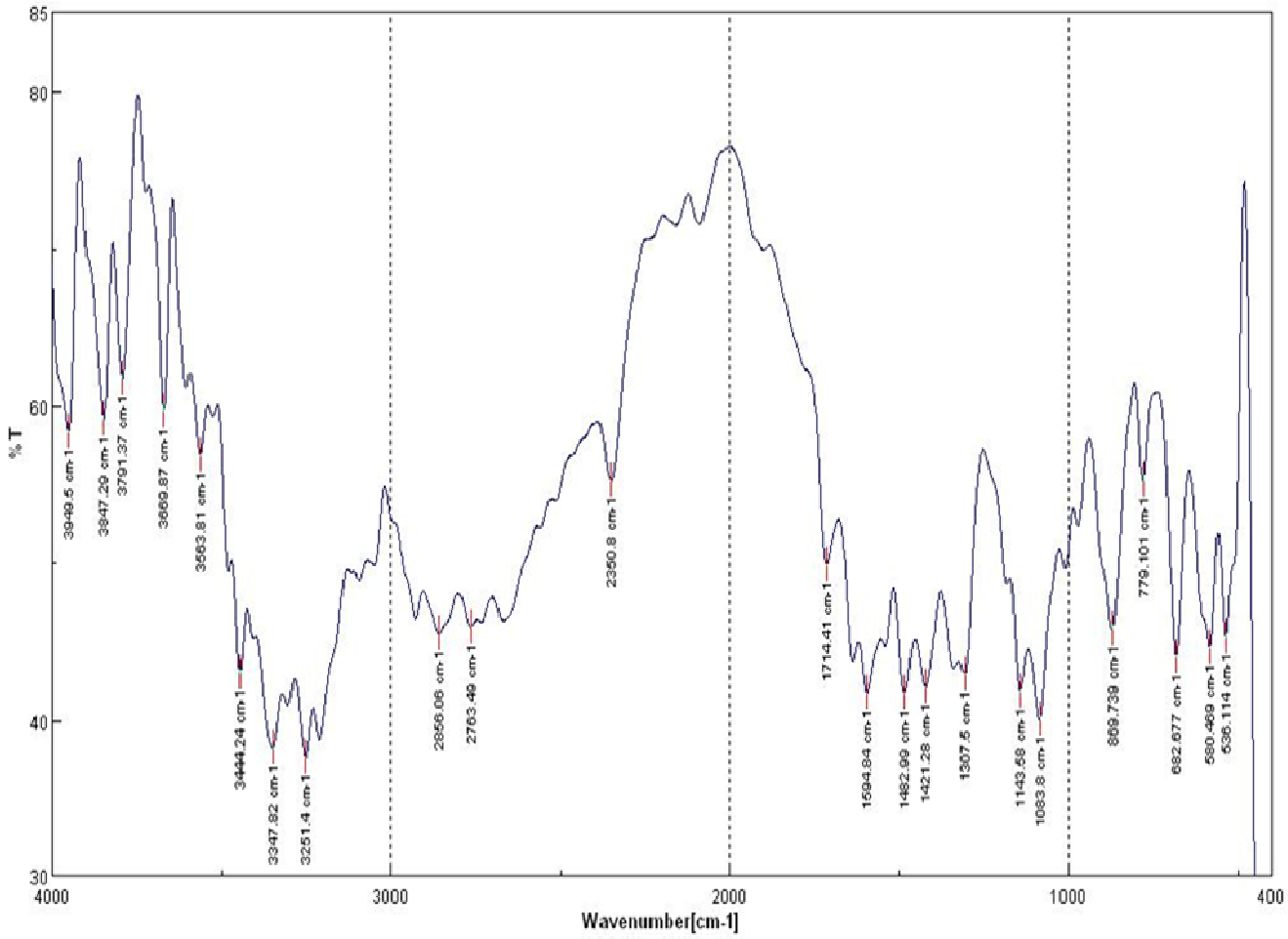

Figure-5
FTIR Spectrum of Pure Acyclovir

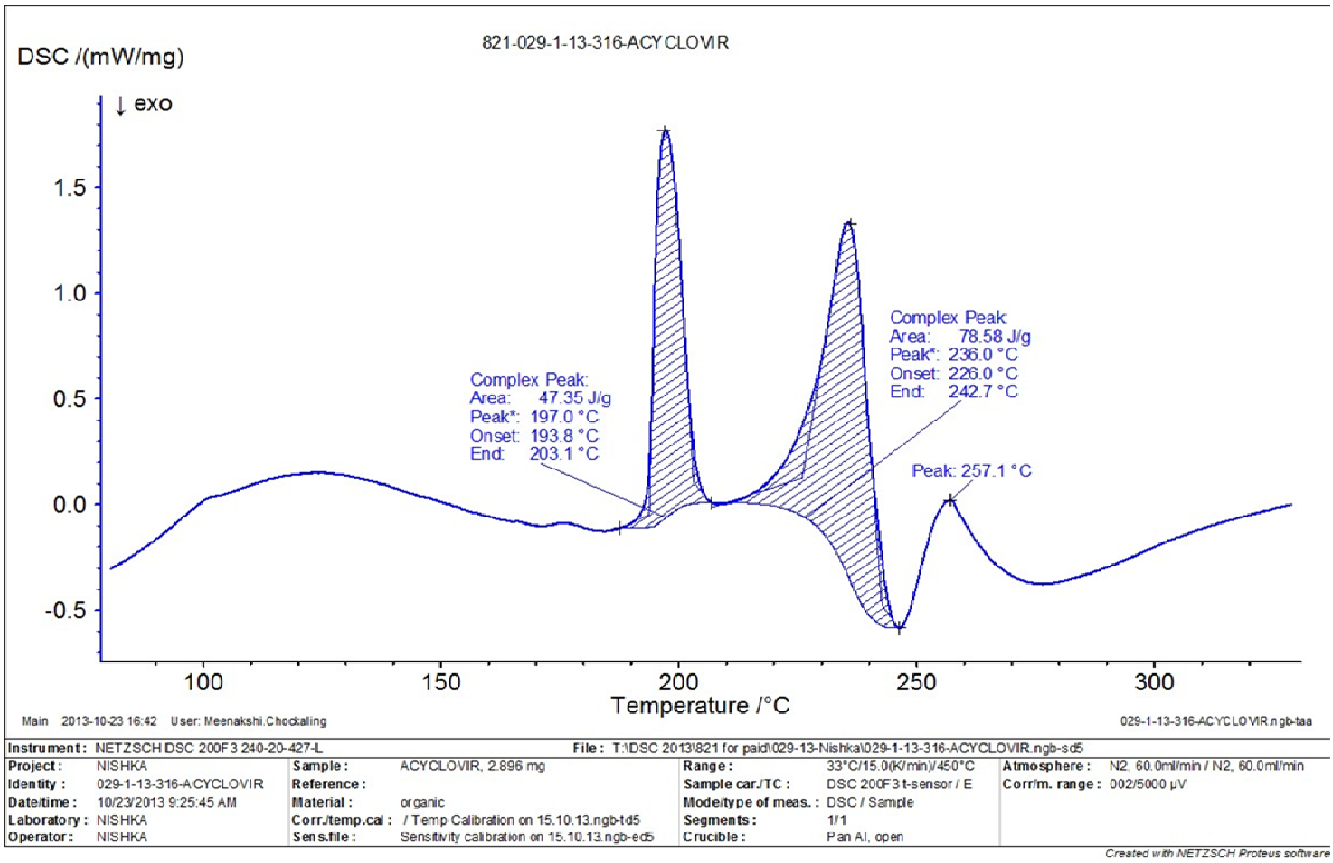

Figure-6
DSC thermo gram of Acyclovir

Evaluation of Pre-Compression Parameters of Acyclovir Matrix Tablets: The bulk density, tapped density, Hausner's ratio, Compressability index and angle of repose for the blend was performed and reported in the table 5. The bulk density for acyclovir blend of entire formulations varied from 4.56±0.006 to 7.89±0.583. Tapped density for acyclovir blend was varied from 4.99±0.066 to 9.11±0.75 respectively. Bulk density and Tapped densities showed good packability of the granules. For acyclovir blend the compressibility index for all formulations ranges from 4.91±0.971 to 19.28±0.144 respectively. ACL7 has lowest Carr's index indicating good compressibility. The Hausner's ratio for Acyclovir blend ranges from 1.086±0.011 to 1.24±0.002. The ACL7 is having lowest hausner's ratio indicating good flow property. Angle of repose for acyclovir blends ranges from 21.16±0.921 to 28.49±0.572 respectively. These represents that the blend flows freely through the hopper.

Formulation of Acyclovir Sr Tablets (Wet Granulation Method): The sustained release tablets were prepared by Wet granulation method**;** all the ingredients were weighed and mixed one by one according to the composition. First the drug, lactose, eudragit, HPMC were added to the mortar and pestle. Thorough mixing was done and the ingredients were passed through #40 mesh. Blended with water to form a damp mass and passed through #20 mesh and dried at 40ºC and lubricants were added. Then the powder blend was compressed on a 9 Station Rotary compression machine by using 6 mm circular shape punches.

Evaluation of Post Compression Parameters for Acyclovir Sustained Release Tablets: The above formulated tablets were evaluated for the following parameters. Thickness of the acyclovir was important for the uniformity of tablet. Thickness was measured using the Vernier callipers. The thickness of Acyclovir tablet for all the formulations were in the range of 2.46±0.312 to 4.347±0.189. The hardness of all the tablets prepared by Direct compression method for acyclovir tablets was within the range of 6.17±0.289 kg/cm^2 to 7.33±0.289 kg/cm^2. Tablet hardness was increased as increasing the compression force. This ensures good handling characteristics of all batches. The friability of all the prepared formulations was within the I.P limit. The % of friability for tablet ranges from 0.44±0.036 to 0.713±0.127 respectively. The results were tabulated in table 7. The % friability was NMT 1% in all formulations ensuring that the all the tablets were mechanically stable.

The weight variation in tablet formulations was in the range of 800.49±1.3 to 1100.48±1.578 mg. All the prepared tablets passed the weight variation test. The weights of all the tablets were found to be uniform with low standard deviation values.

Swelling Index: The diameter of tablets was taken at intervals of five minutes until maximum diameter was attained with a digital Vernier caliper[7,8]. Thereafter the swelling indices (SI) were calculated from initial diameter of tablet (D1) and maximum diameter on swelling in water (D2) as expressed below:

SI (%) = D2/D1 x 100

Table-5
Powder Flow Properties for Acyclovir Sustained Release Tablets

Formulation code	Bulk density ± S.D	Tapped density ± S.D	Hausner's ratio ±S.D	Carr's index± S.D	Angle of repose ± S.D
ACL1	4.57±0.015	5.097±0.058	1.116±0.01	10.393±0.784	24.83±0.865
ACL2	4.58±0.015	5.097±0.061	1.114±0.013	10.194±1.08	22.98±1.06
ACL3	4.56±0.006	5.653±0.011	1.24±0.002	19.28±0.144	22.813±0.949
ACL4	4.57±0.006	5.003±0.047	1.094±0.009	8.589±0.794	19.77±0.782
ACL5	4.58±0.011	4.99±0.066	1.088±0.011	8.079±1.0	24.37±0.754
ACL6	5.56±0.006	6.67±0.052	1.199±0.009	16.588±0.69	28.06±0.398
ACL7	5.58±0.01	6.06±0.053	1.086±0.011	7.915±0.93	23.617±0.647
ACL8	5.57±0.006	6.67±0.011	1.196±0.0008	16.4±0.058	26.49±0.65
ACL9	5.58±0.006	6.657±0.006	1.192±0.002	16.1±0.138	26.64±0.915
ACL10	5.58±0.01	6.64±0.011	1.19±0.001	16.01±0.077	21.16±0.921

Table-6
Different concentrations of Acyclovir SR Tablets

Formulation Code	Drug ACY	SA	XAN	HPMC K 15	MCC	Talc	MAN (QS)	Total
ACY1	400	20	20	150	200	10	200	1000
ACY2	400	20	40	150	210	10	170	1000
ACY3	400	20	80	150	220	10	120	1000
ACY4	400	80	20	150	230	10	110	1000
ACY5	400	40	20	150	240	10	140	1000
ACY6	600	30	30	200	250	10	180	1300
ACY7	600	30	60	200	260	10	140	1300
ACY8	600	30	90	200	270	10	100	1300
ACY9	600	90	30	200	280	10	90	1300
ACY10	600	60	30	200	290	10	110	1300

Table-7
Evaluation of Hardness, Thickness, weight variation, Friability and drug content of Acyclovir Sustained Release Tablets

Formulation Code	Hardness (kg/cm^2)	Thickness (mm)	Avg.wt. of Tablet ±S.D (mg)	Friability ±S.D (%)	Drug Content±S.D (%)
ACL1	6.5±0.5	2.46±0.312	801.86±1.94	0.557±0.275	98.89±0.801
ACL2	6.5±0.866	2.69±0.015	801.18±1.47	0.713±0.127	98.78±0.322
ACL3	6.83±0.764	2.68±0.036	800.8±1.13	0.623±0.03	98.67±0.61
ACL4	6.67±0.289	2.69±0.061	800.49±1.3	0.577±0.042	98.81±0.501
ACL5	6.83±0.764	2.68±0.075	800.47±1.08	0.617±0.11	99.52±0.395
ACL6	7.17±0.764	3.19±0.045	1100.03±1.305	0.577±0.042	99.33±0.45
ACL7	6.5±0.5	3.137±0.064	1100.39±1.32	0.677±0.06	99.05±0.615
ACL8	7.67±0.289	3.167±0.021	1100.5±0.947	0.57±0.06	98.43±0.255
ACL9	6.83±0.289	3.13±0.021	1100.6±1.823	0.577±0.042	98.64±0.367
ACL10	6.67±0.289	3.157±0.015	1099.87±1.39	0.767±0.224	99.04±0.714

Table-8
Swelling Index of Acyclovir Loaded Sustained Release Tablets for ACL1 to ACL10

Time (hrs)	Swelling Index (%)									
	ACL1	**ACL2**	**ACL3**	**ACL4**	**ACL5**	**ACL6**	**ACL7**	**ACL8**	**ACL9**	**ACL10**
0	0	0	0	0	0	0	0	0	0	0
1	69.17	62.24	70.24	79.01	56.07	66.28	60.42	69.8	77.42	73.14
2	73.21	66.1	75.58	88.75	60.29	70.19	65.71	73.62	87.57	81.53
3	80.09	69.26	80.08	96.94	63.04	76.52	66.91	78.72	94.41	89.49
4	89.63	75.48	87.14	86.71	75.71	85.04	73.86	84.81	83.17	98.71
5	97.04	84.12	94.17	77.82	80.94	93.37	81.62	91.18	75.28	86.28
6	86.39	87.09	99.41	73.49	70.64	82.97	84.09	97.64	71.94	80.49
7	81.53	75.03	89.38	66.21	65.01	78.01	71.83	86.24	63.12	75.18
8	77.94	70.97	83.27	62.8	61.53	72	68.04	80.27	60.08	71.83
9	74.82	64.52	78.19	59.13	56.19	69.73	60.82	74.19	57.31	67.19
10	71.17	57.34	72.82	55.82	52.65	67.05	56.17	66.82	52.27	62.25
11	66.38	52.13	69	51.63	51.08	64.81	50.98	63.19	49.34	58.03
12	62.59	47.65	60	48.21	46.7	59.27	46.09	54.28	46.12	53.21

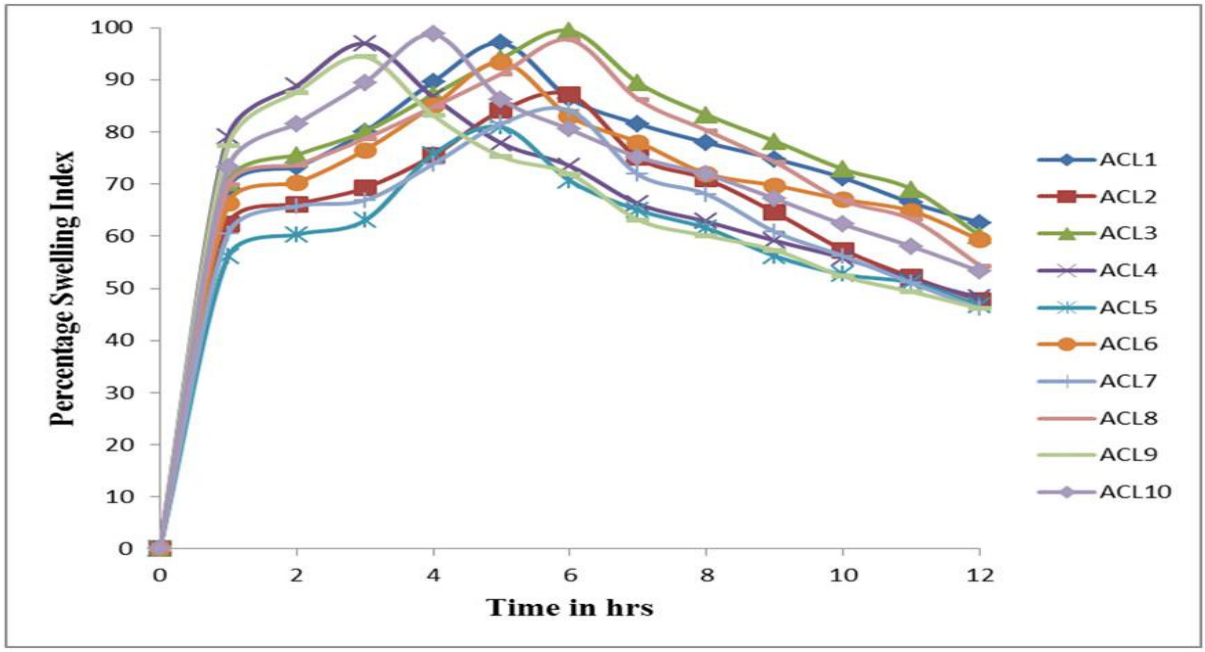

Figure-7
Swelling Index Plot for ACL1 to ACL10

Prediction of Drug Release Mechanism of Acyclovir Can Be Predicted By 'N' Value[9]: i. If 'n' values which is less than 0.45, the drug release mechanism would be Fickian diffusion mechanism. ii. If 'n' value is more than 0.45 and less than 1, the release mechanism would be non - Fickian diffusion. iii. If 'n' value is equal to 1, the drug release mechanism would be case II transport (Zero order release). iv. If 'n' value is more than 1, the release mechanism would be super case II transport.

Table-9
Regression and Slope Data of Release Kinetics of Acyclovir SR Tablets

Formulation code	Mathematical models (release kinetics)					
	Swelling Index (t=12 hrs)	Zero order kinetics	First order kinetics	Higuchi's	Peppa's	
		r^2	r^2	r^2	r^2	n
ACL1	62.59	0.997	0.871	0.926	0.996	1.02
ACL2	47.65	0.998	0.915	0.928	0.997	0.939
ACL3	60	0.998	0.905	0.934	0.997	0.925
ACL4	48.21	0.995	0.797	0.877	0.999	1.12
ACL5	46.7	0.996	0.788	0.903	0.998	1.0
ACL6	59.27	0.996	0.847	0.932	0.996	1.02
ACL7	46.09	0.998	0.912	0.931	0.998	0.954
ACL8	54.28	0.997	0.88	0.94	0.995	0.916
ACL9	46.12	0.995	0.764	0.88	0.999	1.09
ACL10	53.21	0.994	0.715	0.898	0.997	0.975

Summary and Conclusion

The swelling index of all formulation increases as increase the concentration of gum in each formulation. Swelling index of tablets prepared from ACL3 resulted as better swelling behaviour with respect to concentration and as per the linear regression analysis of all the fabricated tablets shown as R2 values in table 9. When the data were plotted according to the first-order equation, for all formulations (ACL1 to ACL10) showed a fair linearity, with regression (R^2) values between (0.685 to 0.915) clearly indicate that drug was not release as per first order mechanism. All the formulation expressed by Higuchi classical diffusion equation as the plot shows linearity with regression coefficient (R2) value as (0.88 to 0.948) also not close to infinity indicate drug release process is not as per Higuchis plot. The zero-order plots of all formulations were found to be highly linear, and close to infinity as indicated by their high regression (R^2) values as (0.994 to 0.998). Therefore it was ascertained that the drug permeation from these formulations could follow either near zero or zero order kinetics. Hence release mechanism was shifted from zero order to Higuchis followed by first order kinetics. In the case of formulation ACL3 with Xanthan gum and sodium alginate shows non-fickian diffusion mechanism with n value as (0.925) therefore diffusion with erosion mechanism play role release from natural gum.

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