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Research Article

OSMOTICALLY REGULATED FLOATING CAPSULE FOR CONTROLLED DELIVERY OF ACYCLOVIR: A WATER-SOLUBLE DRUG

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ABSTRACT

Acyclovir is a guanine analogue used in the treatment of Herpes Simplex Virus(HSV). The aim of the present study was to develop a hydrodynamically balanced system of Acyclovir as single unit floating capsule. This system can remain in stomach for longer period and hence can release the drug over a prolonged period of time. The capsules were cross linked with vapours of Formaldehyde for 24 hours. The formulation was prepared by physically blending method using Acyclovir and osmogent in different ratios. FTIR spectroscopic studies indicated that there were no drug-excipients interaction. Prepared floating capsules were evaluated for floating lag time, total floating time and *in vitro* drug release. As observed the % drug release was increased by increasing in pore size and concentration of osmogent. The optimization was done using 3 factors – 2 level full factorial design. The independent variables were pore size and ratio of osmogent and the response variables were % drug release at 5 hours and 12 hours respectively. The experimental result of optimized batch of floating osmotic capsule demonstrated that % drug release at 5 hours and 12 hours were 40.506and 96.795 respectively. The improved characteristic of selected floating capsule makes them excellent candidates for gastric targeting.

Keywords: Floating osmotic capsule, Acyclovir, *In Vitro* release kinetics and 3^2full factorial design.

INTRODUCTION

Acyclovir is a guanine analogue used in the treatment of viral diseases. The reported oral bioavailability is 15-30% with a plasma elimination half-life of 2-3 h. Acyclovir has its absorption window in the duodenum and small intestine. After per oral administration, only 20% of the drug is absorbed with the remaining 80% of the drug excreted in the feces. After repeated per oral dosing of small amounts of acyclovir the bioavailability can be enhanced. These facts indicate that increasing gastric residence time may enhance bioavailability of acyclovir. Therefore, acyclovir was selected as a model drug for the design of a floating osmotic capsule with a view to improve its oral bioavailability.

Floating Drug delivery system or hydrodynamically balanced systems (HBS) have a bulk density lower than the gastric fluids (<~1.004 g/cm³), and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the Surface of the meal. Floating properties based on the mechanism of buoyancy are divided into: non effervescent systems with inherent low density or low density due to swelling; and effervescent systems with low density due to gas generation and entrapment[6].

MATERIALS AND METHODS

Acyclovir was obtained from Selvok Pharmaceutical Pvt. Ltd, Bilimora Gujarat, India. Sodium Chloride, Lactose monohydrate, Ceto Stearyl Alcohol, paraffin wax and Mannitol were purchased from, Vraj Chemical Pvt. Ltd, Baroda, Gujarat, India. Hard gelatin capsule shells were purchased from Yarrow Chem Products Mumbai- India Gelatin was purchased from Balaji Chemical Pvt. Ltd, Mumbai, India and Standard Gauze syrine was purchased from Iscon surgical Ltd, Ahmedabad, Gujarat, India. All other chemicals and reagents were of analytical grade. Design Expert 10 (trial version) software was used to optimize the formulation.

Preformulation study

These investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product.

Organoleptic properties: The sample of Acyclovir was studied for different organoleptic characteristics.

Powder blend properties

Bulk density: Apparent bulk density was determined by accurately weighed quantity of powder previously passed through 40 # sieve and poured into a graduated cylinder. The bulk density (ρb) was calculated using following equation[2].

$$\rho b = M/Vb$$

Tapped density: The measuring cylinder containing a known mass of blend (M) was tapped till the volume gets constant. The tapped density (ρt) was calculated using following equation[2].

$$\rho t = M/Vt$$

Angle of repose: The accurately weighed powder was taken in the funnel and the height of the funnel was adjusted in such a way the lower tip of the funnel just touched the apex. The powder was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan\theta = h/r$$

Physicochemical properties

Melting properties

The melting point was determined by Open Capillary Method. The temperature at which the drug sample started to melt was denoted as melting point of sample.

Solubility study

The saturated solubility of the drug was determined by adding excess amount of drug in the 10 ml solvents i.e., Distilled water and 0.1 N HCl separately. The amount of Acyclovir dissolved were quantified using UV Spectrophotometric method λmax at 255nm for 0.1 N HCl and 251nm for Distilled water[7].

Partition coefficient study

Determination of partition coefficient of drug was done by shake flask method for 24 hours using double distilled water and *n*-octanol as solvent system. Aqueous phase was separated and after suitable dilution absorbance was recorded on UV spectrophotometry at 251 nm[8].

$$\textbf{Partition coefficient} = \frac{\textit{Amount of drug in organic phase}}{\textit{Amount of drug in aqueous phase}}$$

Preparation of cross linked of hard gelatin capsule shells

Capsule shells of "00" size was kept in the desiccator previously saturated with formaldehyde by opening cap for a period of one day for the cross linking. After a day the shells were taken out and were kept for the air drying for the period of 24 hours. at room temperature in well ventilated area[1].

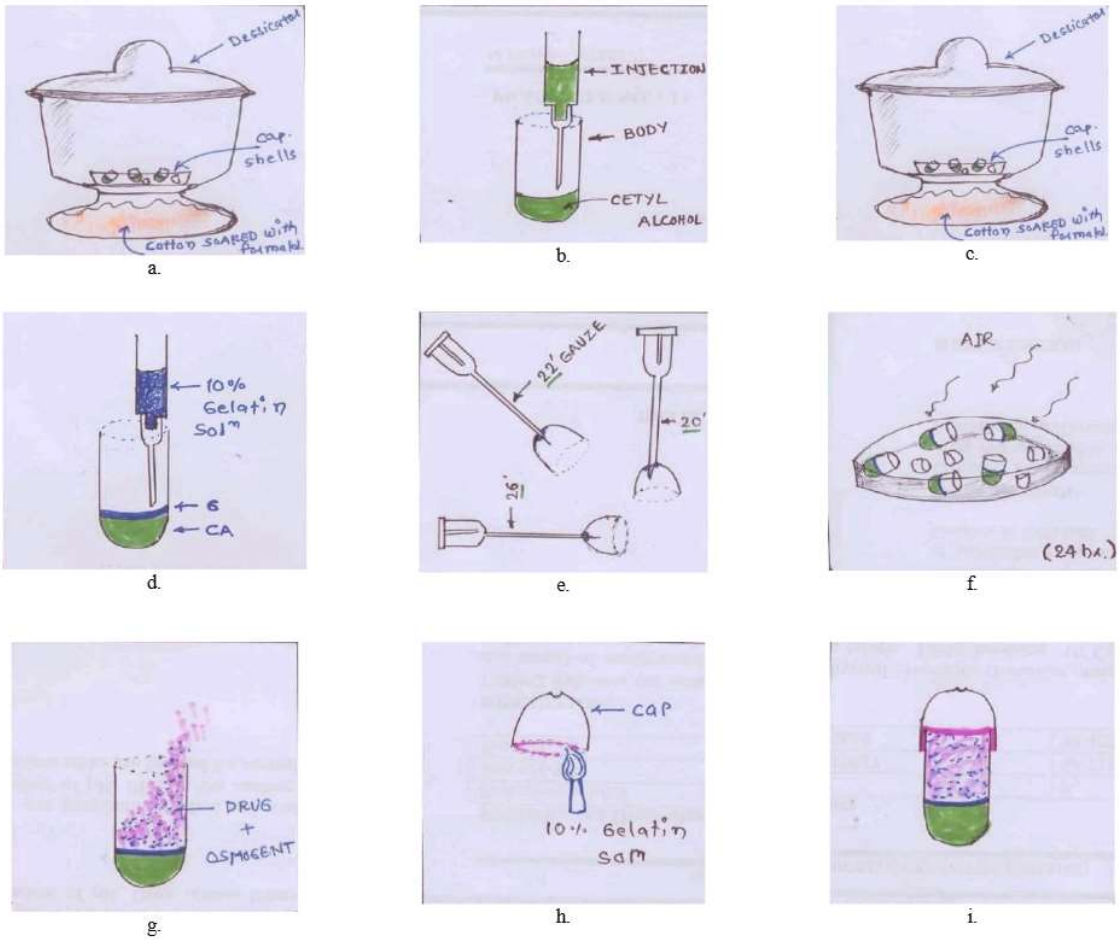

Figure 1 Method of preparation steps for floating capsules

Figure: a. Hard gelatin capsule shells saturated with formaldehyde, b. Filling of cetyl alcohol into body of capsule shell, c. Cross linking period with formaldehyde, d. Filling of waxy material into the body of capsule shell , e. Different gauze size for pore formation , f. Air drying of capsule shell , g. Filling of drug + osmogent mixture, h. sealing of cap portion with body of shell, i. prepared capsule shell

Filling of Waxy material into hard gelatin capsule shell

Accurately weighed 1 gm of Ceto stearyl alcohol in a porcelain dish and kept it for melting in porcelain dish at 40°C in water bath. With the help of syringe 150 mg wax was filled in each of the capsule bodies. Cool it properly for rigidization. 10% gelatin solution was injected as a thin layer over it and cool it properly. Again it was kept for cross linking for 2-days in desiccator with formaldehyde and after 2 days it was air dried for a period of one day at room temperature in well-ventilated area[1].

Preparation of drug releasing orifice in the capsule shell

Orifice was prepared with the help of standard gauze syringe in the cap portion.

Filling of drug and osmogent

The Drug and Osmogent were precisely weighed as per the formula, passed through 40 mesh sieve and mixed homogeneously. This mixture was filled in the capsule body with the help of spatula. The final quantity i.e., 500 mg was maintained using mannitol as diluent in each formulation[1].

Sealing of filled capsule

After filling lock, the body part with cap and seal it with 10 % gelatin solution to ensure the system is elementary osmotic type delivery and to check that the capsule cap and body does not open or break at joint[1].

Preliminary screening

The purpose of the preliminary study was to optimize the formulation which having best drug release and to check the buoyancy of dosage form. Five different experimental variables were selected like amount of osmogent, ratio of osmogent, degree of cross linking, pore size and amount of floating agent which affects the drug release and buoyancy parameters.

1. Cross linking with formaldehyde for periods of 1, 2 or 3 days.
2. Ceto stearyl alcohol as floating agent ranging from 50 mg to 200 mg to check the effect on buoyancy.
3. Pore size by making the pores with different gauzes ranging from (18', 22', 26') were utilized.
4. To check the effect of osmogent sodium chloride and lactose were used. The drug was taken in the quantity of 200 mg with quantity of NaCl was 100(P1), 150 (P2), 200 (P3) and 250 (P4) mg while two batches with 300 (P5) and 400 (P6) mg lactose were prepared; in all the batches mannitol was taken as diluent to make up the quantity up to 500 mg.
5. In the case of ratio of osmogent quantity was taken as 50:50 (P7) and 25:75 (P8) (sodium chloride to lactose) and its effect on the release was evaluated.

Table 1: Preliminary screening batches

Batches	P1	P2	P3	P4	P5	P6	P7	P8
Acyclovir	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
NaCl (Sodium chloride)	100 mg	150 mg	200 mg	250 mg	-	-	125 mg	62.5 mg
Lactose monohydrate	-	-	-	-	200 mg	300 mg	125 mg	187.5 mg
Mannitol	200 mg	150 mg	100 mg	50 mg	100 mg	-	50 mg	50 mg

Experimental design

A 3^2 full factorial design in present study to evaluate the effect of independent variables and dependent variables. In this design, 2 factors were evaluated, each at 3 levels, and experimental trials were performed for 9 possible combinations. The pore size (X_1) and ratio of osmogent (X_2) were chosen as independent variables in 3^2 full factorial design, while Y % drug release (% drug release after 5 and 12 hours respectively) and were taken as dependent variables.

Table 2: Independent variables and their levels

Independent variables	Level		
	Low (-1)	Medium (0)	High (+1)
X1: Pore size (gauze size)	0.45 mm[Inner] 13 mm[outer] (26')	0.7 mm[Inner] 25 mm [outer] (22')	1.2 mm [Inner] 38 mm [outer] (18')
X2: Ratio of NaCl/Lactose monohydrate	25:75	50:50	75:25

Optimization

The aim of pharmaceutical formulation and development was to develop an acceptable formulation in shortest period of time and using minimum trials.

Table 3: Batches of 3^2 full factorial design

Batch no.	Gauze size	Drug (mg)	NaCl (mg)	Lactose monohydrate (mg)	Mannitol (mg)
F1	(0.45mm)	200	62.5	187.5	50
F2	(0.45mm)	200	125	125	50
F3	(0.45mm)	200	187.5	62.5	50
F4	(0.7 mm)	200	62.5	187.5	50
F5	(0.7 mm)	200	125	125	50
F6	(0.7 mm)	200	187.5	62.5	50
F7	(1.2 mm)	200	62.5	187.5	50
F8	(1.2 mm)	200	125	125	50
F9	(1.2 mm)	200	187.5	62.5	50

Evaluation parameters
***In vitro* buoyancy studies**

The capsules were prepared and placed in 900 ml 0.1N HCl. Four different concentration of floating agent were taken ranging from 50, 100, 150 and 200 mg. The time required to float was considered as floating lag time while the time period for which it remains buoyant was taken as the total floating time[9].

***In vitro* dr9/*–ug release studies**

In vitro release studies were carried out using conditions USP dissolution apparatus USP (Type II) paddle; dissolution medium 900 ml at 50 rpm and 37 ± 0.5° C. Aliquots of 10 ml sample has been withdrawn from dissolution medium at predetermine time and filtered through Whatman filter paper no. 41 and absorbance of filtered were measured at 255 nm[10].

RESULTS AND DISCUSSION
Preformulation study
Organoleptic study

The sample of Acyclovir was studied for organoleptic characters and it was found to be White or almost white crystalline powder.

Table 4: Organoleptic properties of drug

Parameters	Observation
Colour	White
Odour	Characteristic
State	Crystalline powder

Powder blend properties

The values of angle of repose, bulk density and tapped density of powder were fall within the acceptable range of flow properties which indicates good packing properties of powder.

Table 5: Flow properties of powder and blend

Parameter	Result			
	Acyclovir	Lactose monohydrate	Mannitol	NaCl
Bulk density (gm/cm^3)	0.373 ± 0.04	0.69 ±0.053	0.751 ± 0.019	0.798 ± 0.012
Tapped density (gm/cm^3)	0.57 ± 0.01	0.131 ±0.041	0.941 ± 0.029	0.154 ± 0.192
Angle of repose	43.38 ± 1.29	28.06 ±0.201	23.36 ± 2.910	29.65 ± 0.225

Physicochemical properties of drug

Melting point: Melting point of Acyclovir, was determined by capillary rise method and was found to be 256 – 260°C (Reported 256.5 – 257°C). It was confirmed that obtained drug sample having good agreement with official valuesand found to be in the pure form.

Table 6: Melting point of drug

Observed melting point	256 – 260°C
Reported melting point	256.5 – 257°C

Solubility study: Solubility of acyclovir was carried out in distilled water as well as in 0.1 N HCl. The result was complying with reported data.

Table 7: Solubility stud of drug

Solvents	Solubility (mg/ml)	
	Observed	Reported
Distilled Water	3.125 mg/ml	2.5 mg/ml
0.1 N HCl	32.6 mg/ ml	30 mg/ml

Partition coefficient: The *n*-octanol/water partition coefficient was found to be -1.21 ± 0.21 which indicate that the drug has hydrophilic characteristic which was close to reported value of partition coefficient i.e. -1.56.

Table 8: Partition coefficient data

System	Partition coefficient of drug sample	Reported partition coefficient
***n*-Octanol: water**	-1.21 ± 0.21	-1.56

Preliminary study

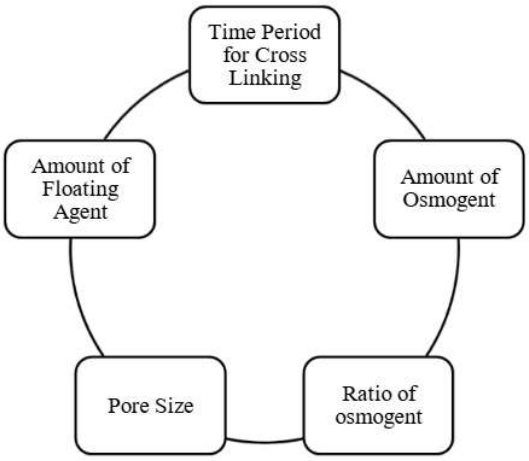

Figure 2 Different variables

Degree of cross link

Hard gelatin capsule shells of "00" size were kept in the desiccator previously saturated by formaldehyde. Cross linking of the capsule was carried out for one, two and three days and their solubility were checked in 0.1 N HCl (stomach pH) for 24 hours. From that the capsule of 1st and 2nd day remain in stomach pH for 7-10 hours whereas, the capsule which is of 3rd day remain in stomach pH for more than 12 hours.

Amount of floating agent

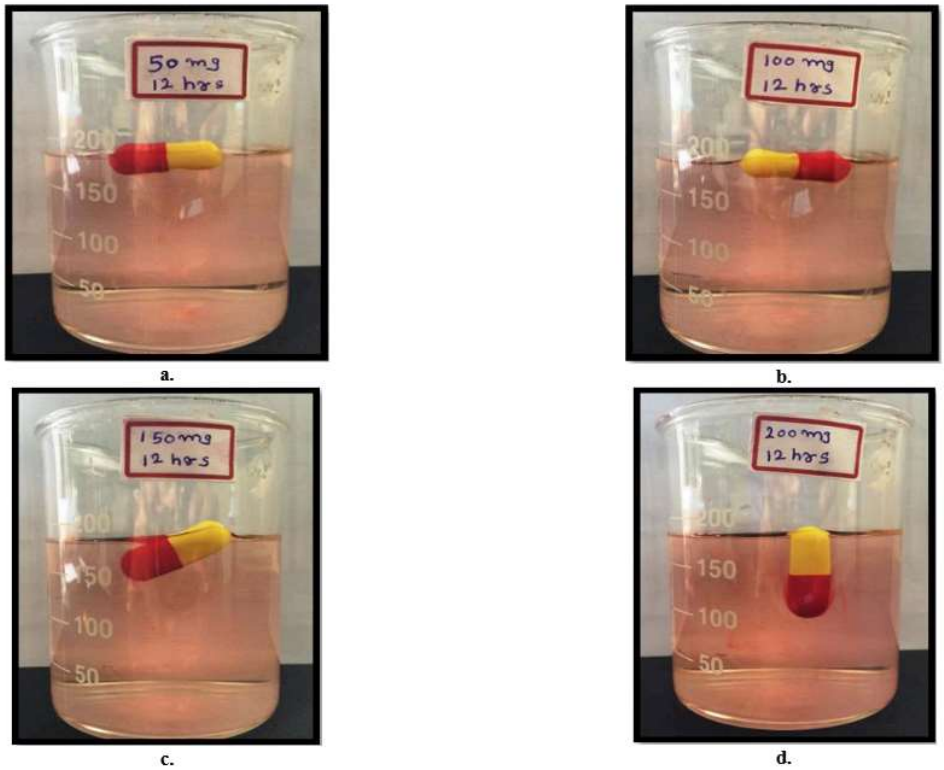

Figure 3 Capsule in 0.1 N HCl

In case of 50 mg of ceto stearyl alcohol first capsule sink then after 2 and half hour and it floats again, while no lag was found in higher amount. Hence it was decided to go for 100 mg of ceto stearyl alcohol with no lag time and to decrease the number of formulation variables.

Pore size

In order to increase the precision and accuracy and to get more reproducibility pores in the cap of the capsule shells were prepared with standard gauze. Figure 3shows the different standard gauze with its outer and inner diameters.

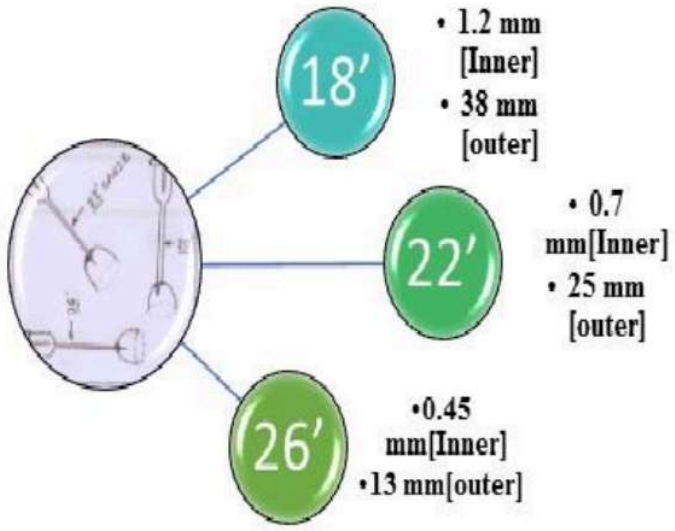

Figure 4 Different size of needle and pore size

Preliminary screening

Amount of osmogent

Sodium chloride in quantities ranging from 100 mg to 250 mg were evaluated at 12 h. The drug release was found to be 22 % in P1 which was 26 % in P2. With 200(P3) and 250 (P4) mg NaCl the drug release ware 38 and 75 % respectively. Another osmogent evaluated was lactose monohydrate with 300 (P5) and 400 (P6) mg of lactose monohydrate and the release were found to be 29 and 64 % at 12 h. The drug release was found to be slower but with good linearity and zero order characteristics.

Ratio of osmogent

The results checked with the amount of osmogent especially with sodium chloride was insufficient with respect to zero order characteristics. With respect to lactose monohydrate the release was very slow but it was zero order. Hence various ratios of sodium chloride to lactose monohydrate (50:50 and 25:75) have been selected and its effect was found to be significant on drug release with zero order profile.

Experimental design

***In vitro* drug release using 3^2 full factorial design**

Table 9: Comparative cumulative % Drug release data of formulation (F1-F9)

Time (Hours)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	1.159 ± 1.134	1.657 ± 2.055	2.396 ± 1.065	2.767 ± 1.234	3.592± 1.135	4.197± 2.094	4.565± 1.232	4.957 ± 2.143	5.606 ± 1.069
2	7.151 ± 1.041	8.307± 1.820	8.307 ± 1.320	9.720 ± 1.340	11.332± 1.320	12.366 ± 1.345	15.413± 1.750	18.819 ± 2.128	19.535 ± 1.473
3	13.545 ± 2.140	15.559 ± 2.245	18.548 ± 2.156	20.825 ± 1.436	22.841± 1.445	25.617± 1.231	27.599 ± 1.520	26.407 ± 2.315	27.700 ± 1.346
4	24.518 ± 1.025	24.277 ± 1.240	25.478 ± 1.252	28.0195± 1.658	30.389± 1.835	31.930 ± 1.745	33.855 ± 1.564	34.868 ± 1.829	35.946 ± 1.693
5	30.542± 2.246	30.784 ± 1.112	31.874 ± 2.138	34.874 ± 1.135	38.995 ± 1.630	39.548 ± 1.445	40.271 ± 1.439	40.942 ± 1.789	41.439 ± 1.554
6	36.985 ± 1.188	37.925 ± 2.037	38.592 ± 1.364	38.951± 2.036	40.721 ± 1.736	42.584 ± 2.132	48.876 ± 1.731	49.219 ± 1.665	49.369 ± 1.683
7	42.439± 2.164	44.795 ± 1.592	45.687 ± 1.335	47.884 ± 1.230	49.293 ± 1.440	51.732 ± 1.253	54.221 ± 1.636	54.369 ± 2.131	55.893 ± 1.836
8	46.419 ± 1.541	48.777 ± 1.725	50.219 ± 1.764	53.401 ± 1.881	55.431 ± 2.165	57.133 ± 1.680	62.855 ± 1.820	63.134 ± 1.981	66.396± 2.057
9	50.649 ± 1.347	52.643 ± 0.947	54.536 ± 1.910	57.138± 2.420	59.714 ± 1.220	62.845 ± 1.520	75.374 ± 1.542	77.373 ± 1.630	79.166 ± 2.115
10	56.377 ± 2.053	57.774 ± 1.353	60.963 ± 2.345	62.132 ± 2.145	65.888 ± 1.357	68.086 ± 1.639	80.259 ± 2.163	81.216 ± 1.865	82.798 ± 1.834
11	62.765 ± 1.735	64.329 ± 2.036	66.901 ± 2.168	68.358± 2.288	70.712 ± 1.721	77.888 ± 1.453	87.881 ± 1.245	89.913 ± 1.651	90.754 ± 1.739
12	68.568± 1.050	70.364± 2.289	72.885± 2.247	75.228± 2.145	77.402± 1.639	87.687± 2.193	92.319 ± 1.521	95.210± 1.985	99.484 ± 1.698

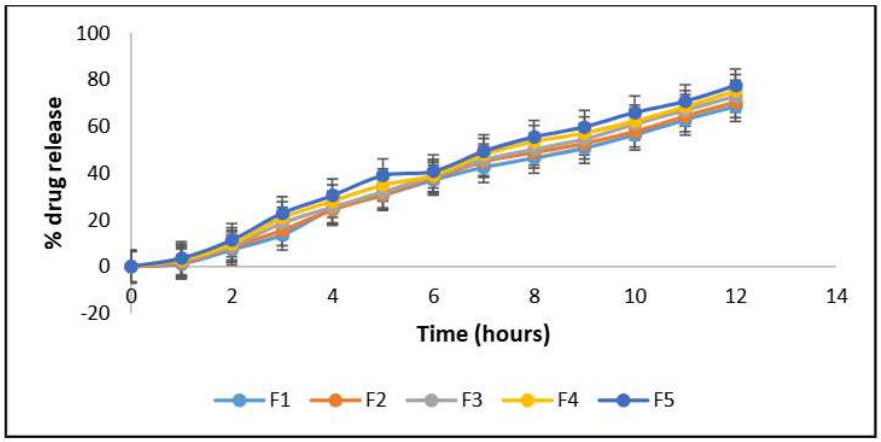

Figure 5 Graph of % drug Release of F1 – F5

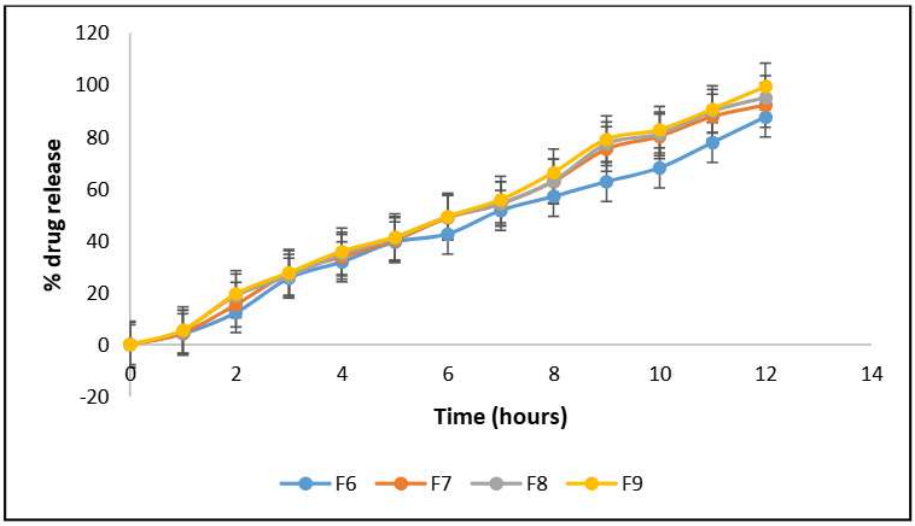

Figure 6 Graph of % drug Release of F6 – F9.

The prepared formulations were controlled the drug release for a period of 12 hours. A good degree of linearity was observed in almost all the formulation. Pore size also having a strong impact on the drug release which is clearly observed in release profile.

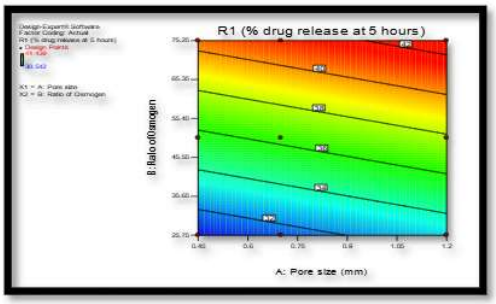

Figure 7 Contour plot of drug release at 5 hours

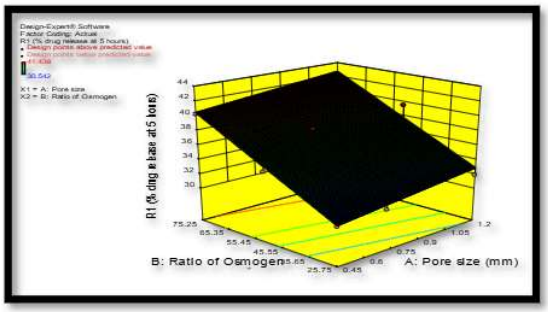

Figure 8 3D mesh graph of % drug at 5 hours

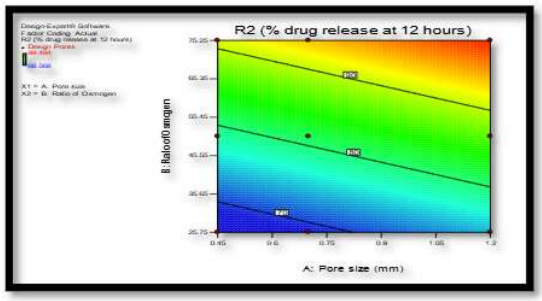

Figure 9 Contour plot of drug release at *5* hours

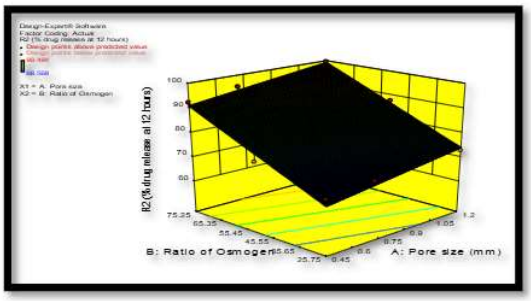

Figure 10 3D graph of drug release at 12 hours

Optimization of design batch by design expert software (trial version)

The optimum formulation was selected based on the criteria of attaining the minimum and the maximum cumulative percentage drug release in 5h (Y1), 12 h (Y2). An overall desirability function dependent on all the investigated formulation variables were used to predict the ranges of variables where the optimum formulation might occur. The desirable ranges are from zero to one (least to most desirable, respectively.

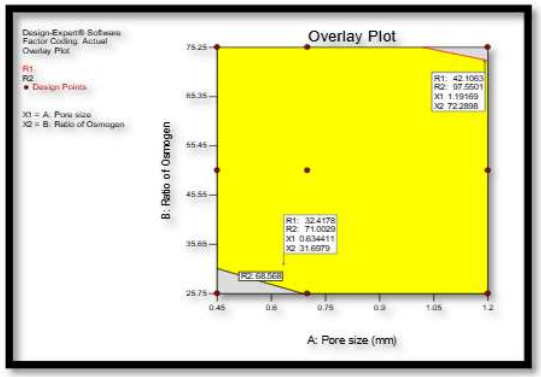

Figure 11 overlay plot for prediction of optimized batch

Table 10 Drug release data for optimized batch

Time (hours)	% Drug Release of optimized batch
0	0
1	2.228 ± 1.349
2	10.696 ± 2.112
3	28.063 ± 2.271
4	33.289 ± 2.461
5	40.506 ± 2.309
6	45.194 ± 1.191
7	58.147 ± 0.655
8	65.143 ± 2.197
9	73.285 ± 1.089
10	80.172 ± 2.731
11	89.413 ± 1.093
12	96.795 ± 2.488
y = 8.7187x - 6.1481 R^2 = 0.9933	

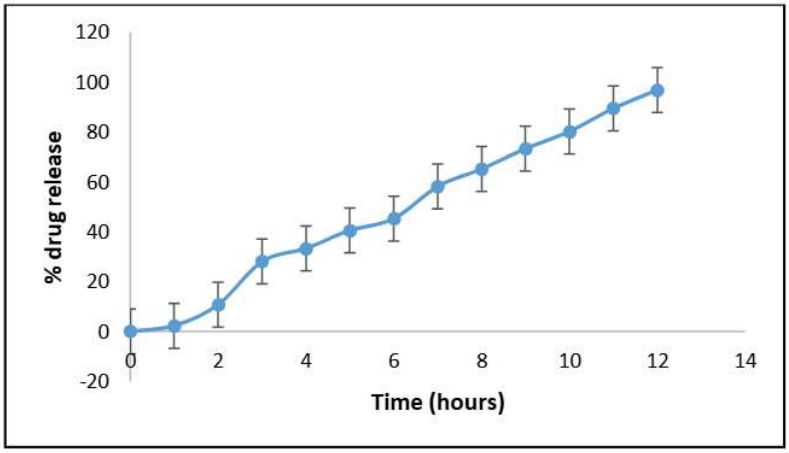

Figure 12 Graph of % drug release of optimized batch

The drug release at 5 h and at 12 h were found to be 40.506 and 96.795 % respectively which were nearer to the predicted values (42.106 and 97.550 %).

CONCLUSION

The present work was aimed to formulate a novel floating osmotic capsule of Acyclovir using the principles of osmosis which will bring down its dosing frequency to once a day. It also encompasses the concept of floating providing prolong gastric residence. The osmotic capsule will be retained in the stomach

and drug will continuously release at the site of absorption thereby improving the therapeutic efficacy of the treatment.

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