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Research Article

ENHANCEMENT OF SOLUBILITY AND OPTIMIZATION OF ORALLY DISINTEGRATING FILMS OF ACYCLOVIR

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ABSTRACT

Objective: The objective of this work was to prepare and optimize orally disintegrating films of acyclovir (ACV), which is a known antiviral agent. To enhance the solubility of ACV, solid dispersions of ACV were made.

Methods: The films were prepared using a solvent casting technique. Full factorial design was utilized for the optimization of the effect of independent variables such as the amount of hydroxypropyl methylcellulose 5 cps, sodium starch glycolate, and propylene glycol on the disintegration time. Other evaluation tests such as drug release, drug content, thickness, and folding endurance of film were also conducted.

Results: Compatibility studies by Fourier transform infrared showed that there was no significant interaction between the drug and excipients used. Disintegration time was found to be 43 s for the optimized batch. The *in vitro* release profile of formulation response disintegrating time in phosphate buffer pH 6.8 revealed that there was a significant increment in drug release of the optimized batch in comparison to the screening batches. Further, short-term accelerated stability studies carried out for 4 weeks for the optimized formulation which proved that the formulated films were stable at the accelerated conditions of temperature and humidity (40±2°C/75±5% RH).

Conclusions: It was concluded that such ACV solid dispersion films could be beneficial in enhancement of dissolution and consequently the oral bioavailability of ACV.

Keywords: Acyclovir, Factorial design, Oral disintegrating films, Solid dispersion, Solubility enhancement.

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INTRODUCTION

In recent times, there has been an augmented requirement for patient-compliant dosage forms. Consequently, the demand for innovative and patient-friendly dosage forms is forecasted to be the whopping US $15,984.3 billion by the end of 2024 up from the US $7,337.8 million in 2015 [1]. Fast-dissolving dosage forms were initiated in the past century in the seventies as a substitute to tablets, capsules, and syrups for pediatric and geriatric patients who have trouble swallowing conventional oral solid-dosage forms. The popularity of oral dosage forms is evidently because of the patient compliance, ease in administration, and accurate dosing, price, and superior longevity in terms of stability. Oral films are one such patient-friendly dosage forms. Fast or rapidly disintegrating film is conveniently placed on the tongue where it disintegrates. If it is required, the formulation can be designed to quickly disintegrate releasing the medication without delay. This would present the drug in a liberated form to the gastrointestinal tract where the absorption is quickened. Oral dissolving films have the added benefit of not needing a glass of water for administration [2]. Orodispersible films have been successfully formulated and evaluated for drugs such as metoclopramide [3]. Different polymers have been used for making oral films such as hydroxypropyl methylcellulose (HPMC) and sodium carboxymethylcellulose [4].

Acyclovir (ACV) is an antiviral agent, which is indicated chiefly for the treatment of infection arising due to herpes simplex virus, chickenpox, and shingles. ACV is known by its IUPAC name as 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one [3]. Its half-life is reported to be 2–4 h and protein binding to be 9–33%. Water solubility is poor at 2.5 mg/ml. In humans, the average oral bioavailability of ACV after administration of a 200 mg dose is approximately 20%, and this decreases to about 10% with 800 mg dosing [5]. Due to its this low oral bioavailability, achievement of plasma concentration sufficient for inhibition of the less sensitive herpes simplex virus is not easy and intravenous administration may be obligated for better efficacy. Solubility enhancement has been positively linked to increased oral absorption [5]; hence, in the present research, an attempt has been made to improve the solubility of ACV by making ACV solid dispersions (ACV-SDs) and formulating ACV-SD into oral films.

MATERIALS AND METHODS

Materials

ACV was a gift sample from Atul Limited, Gujarat, India, mannitol purchased from Loba Chemie, Mumbai, India, dimethyl sulfoxide (DMSO), polyvinylpyrrolidone K 30, glycerol purchased from Thermo Fisher Scientific, Bangalore, India, HPMC 5 cps HPMC K15, ethanol, sodium starch glycolate (SSG), propylene glycol, sodium hydroxide, and potassium dihydrogen phosphate purchased from SD Fine-Chem Ltd., Mumbai, India.

Equipment

Bath sonicator - Sidilu renewable energy, Bangalore, India; Digital balance – Ohaus, India; pH meter - Analytical technologies Ltd., Gujarat, India; UV Visible spectrophotometer - Shimadzu, Corporation, Japan; Disintegration apparatus -Electrolab, Mumbai, India; 8-station dissolution apparatus, LabIndia disso 8000, India; Fourier transform-infrared (FTIR) spectrometer - Bruker, USA; Hot air oven - Techno scientific, Bangalore, India.

Methodology

Preformulation studies

Solubility of ACV

The solubility of ACV was checked in ethanol, DMSO, water, phosphate buffer solution (PBS), and pH 6.8 using the shake-flask technique

Table 1: Preliminary trial batches for preparing of blank films

S. No.	Ingredients	Batches						
		T1	T2	T3	T4	T5	T6	T7
1	HPMC K15 (mg)	250						
2	HPMC M (mg)		250					
3	HPMC 100 (mg)			250				
4	HPMC 5 cps (mg)				250			
5	HPMC E (mg)					250		
6	PVP K 30 (mg)						250	
7	HPMC 5 cps: HPMC K15 (mg)							250:250
8	Glycerol (mg)	200	200	200	200	200	200	200
9	Vehicle q.s 10 ml	Water	Water	Water	Water	Water	Water	Water

HPMC: Hydroxypropyl methylcellulose, PVP: Polyvinylpyrrolidone

[6]. Briefly, an excess amount of ACV was added to 5 ml of each of the above liquids and shake for 48 h to achieve equilibrium, then filtered through Whatman filter paper #1 and analyzed spectrophotometrically at λ_{max} 252 nm.

Compatibility studies

The FTIR spectrum of ACV was generated using the potassium pellet method. A little quantity of the drugs ACV was intimately mixed with potassium bromide (preheated at 105° for 1 h in an oven). Then, the mixture was made into a disc using a press machine. The disc was then analyzed to generate the FTIR. Similarly, ACV-excipient mixture was also studied.

Preparation of solid dispersion

The carrier used was mannitol. Solid dispersion was prepared by coevaporation of equimolar ACV - mannitol in dimethyl sulfoxide solution on the water bath 70–90°C. Each solid product after complete evaporation of solvent used was then scrapped off, pulverized, and sieved through 80#. The preliminary trial batch is shown in Table 1.

Formulation of blank mouth dissolving films

Formulation trial T4 showed good film-forming properties than other formulation; hence, HPMC 5 cps was selected for further film formulation.

Formulation of fast disintegrating film of ACV-SD

Weighed amount of film-forming polymer was added to water and stirred at a rotation of 100–120 rpm using magnetic stirrer. ACV-SD containing equivalent amount of drug (200 mg) was then added into the solution with magnetic stirring for 2–3 min at rotation speed of 150–200 rpm. Other excipients such as plasticizer and superdisintegrant were then added one by one with continuous stirring. The solution mixture was then slowly poured into a Petri plate, and solvent was allowed to evaporate at a temperature of 60°C using hot air oven overnight. After solvent was evaporated completely, the strip was slowly peeled.

Formulation of screening batch

To identify the vital factors affecting the desired response, a screening design was followed. The screening batches were formulated based on the definitive screening design done with the help of statistical software JMP® 11 by SAS for three factors - the amounts of HPMC (5 cps), SSG, and glycerol (plasticizer). The design was performed for eight experimental runs with the amounts of HPMC 5 cps and SSG ranging from 250 to 500 mg and 5 to 20 mg, respectively. These ranges were decided based on a prior literature survey. Evaluations of these batches were performed the screening batches are shown in Table 2.

Based on the result of screening batches, an optimized formulation (Table 3) was designed and evaluated for disintegration time.

Table 2: Screening batches of ACV-SD

S. No.	ACV-SD (mg)	HPMC 5 cps (mg)	Plasticizer	SSG (mg)	Water (ml)
			Glycerol (ml)		
F1	200	250	0.25	20	10
F2	200	500	0.25	20	10
F3	200	500	0.25	5	10
F4	200	250	0.5	20	10
F5	200	250	0.25	5	10
F6	200	250	0.5	5	10
F7	200	500	0.5	5	10
F8	200	500	0.5	20	10

HPMC: Hydroxypropyl methylcellulose, ACV-SD: Acyclovir solid dispersion, SSG: Sodium starch glycolate

Table 3: Optimized formula

S. No.	Factor	Amount
1	HPMC 5 cps (mg)	375
2	SSG (mg)	11.912
3	Glycerol (ml)	0.375

HPMC: Hydroxypropyl methylcellulose, SSG: Sodium starch glycolate

Table 4: Solubility studies of acyclovir and solid dispersion

S. No.	Solvent	Solubility (mg/ml)
1	Ethanol-SD	2.447
2	DMSO-SD	45.54
3	Water-SD	4.74
4	pH 6.8-SD	29.64
5	Ethanol-PD	5.69
6	DMSO-PD	40.41
7	Water-PD	24.93
8	pH 6.8-PD	0.355

DMSO: Dimethyl sulfoxide

Evaluation studies of orally disintegrating films of ACV

Thickness

The thickness of films was measured using screw gauge at three different points of the film and an average was taken.

Drug content

2.5 cm^2 containing 2.5 mg of ACV was cut evenly and grinded. It was then added to 100 ml volumetric flask and diluted using PBS pH 6.8. It was then sonicated for 15–20 min. A further dilution was made to Beer's range and the absorbance was measured using UV spectrophotometer at 252 nm λ_{max}.

Folding endurance

Area of films (4.5 cm×2.5 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the films could be

folded the same place without breaking gave the exact value of folding endurance.

Disintegration time

A small strip of film is placed in beaker containing 15 ml of phosphate buffer pH 6.8 and continuously shaken until the strip disintegrates completely.

Surface pH

Surface pH of film was determined by placing the film on the surface of 1.5% agar gel followed by placing pH paper (pH range 1–11) on the films. The change in the color of pH paper was observed.

In vitro release studies

An area of film containing equivalent amount of ACV (2.5 mg) cm^2 was weighted and added to 900 ml of phosphate buffer pH 6.8 (USP-II dissolution apparatus) at 37°C using at a rotation speed of 50 rpm. 5 ml sample was withdrawn at an interval of 5, 15, 30, 45, and 60 min. An equal amount of fresh dissolution medium was added back, respectively, at each time interval after withdrawal of the test sample. Test sample was filtered through Whatman filter paper no 1 and suitably diluted. The absorbance of the diluted sample was estimated for amounted of ACV dissolved by measuring in UV spectrophotometer at 252nm λ_{max}.

Drug-excipients interaction studies

FTIR spectroscopy

An FTIR spectrum was used to identify if any interaction existed between ACV and excipients used. Sample was analyzed by potassium bromide pellet method in an IR spectrophotometer (Bruker) in the region between 4000 and 400/cm.

Table 5: Evaluation of screening batches

S. No.	Code	Thickness (μm)±SD (n=3)	Folding endurance±SD (n+3)	Surface pH±SD (n=3)	Disintegration time (S)±SD (n=3)
1	F1	85.66±3.055	84.66±3.68	7.073±0.030	44.33±3.299
2	F2	65.66±2.081	85±3.55	7.4±0.1632	40.33±2.054
3	F3	86.33±2.081	90±4.08	7.33±0.049	49.33±1.699
4	F4	95±2	100±4.082	7.46±0368	37.66±2.054
5	F5	80±2	93±2.160	7.25±0.142	42.66±2.054
6	F6	90.33±2.51	83±2.160	7.46±0.169	50.33±1.699
7	F7	86.66±1.527	92.33±2.35	7.33±0.265	42.33±2.494
8	F8	77.66±1.524	90.33±2.054	7.21±0.0205	52.33±2.054

SD: Standard deviation

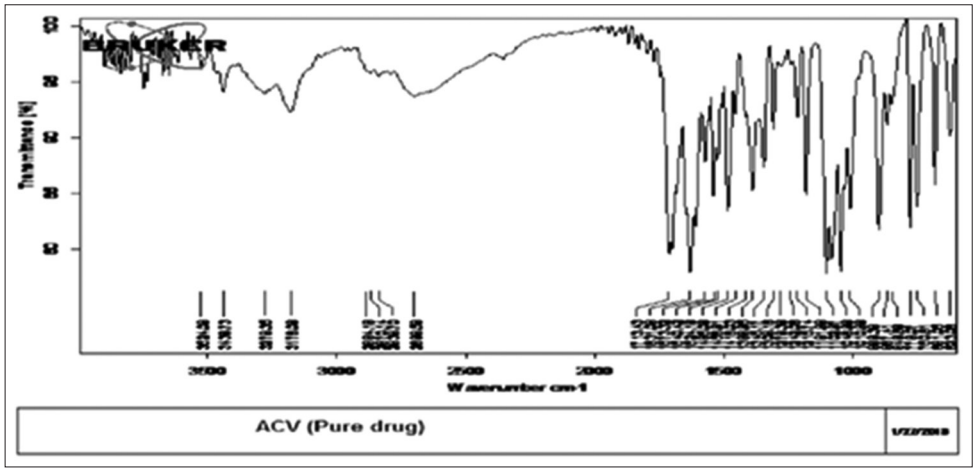

Fig. 1: Fourier transform-infrared spectrum of acyclovir (pure drug) after compatibility study

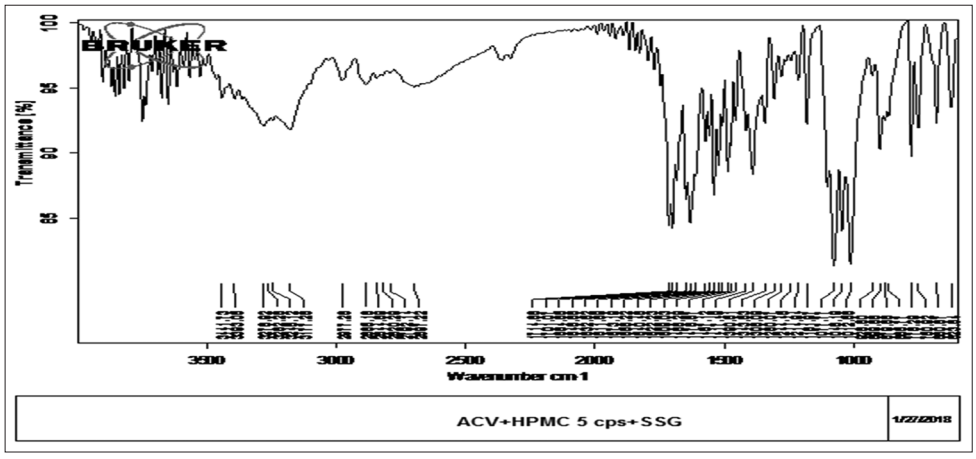

Fig. 2: Fourier transform-infrared spectrum of acyclovir-excipients after compatibility study

Short-term accelerated stability studies

Stability studies accelerated were carried out for the optimized formulation which was kept at 40°C±2°C/75% RH for 1 month. The percentage drug release and drug content were calculated at the end of 30 days, and FTIR was also recorded.

RESULTS

Table 4 summarizes the data for the solubility studies of ACV-SD. Figs. 1 and 2 present FTIR spectra for the compatibility study.

Table 5 summarizes the results of the screening batches. Fig. 3 and Table 6 present the results of the optimized formulation.

Statistical analysis

Tables 6-16 and Figs. 4-10 deal with the results of optimization.

Optimization

Y=Response disintegration time (s)

Singularity details: Intercept=0.005×Drug (mg)=0.1×Solvent (ml)

The comparative *in vitro* release profile before and after short-term accelerated stability study is presented in Fig. 11, while the FTIR of the optimized formulation is shown in Fig. 12.

Table 6: Summary of fit

R^2	0.147204
R^2 Adj	−0.49239
Root mean square error	6.357258
Mean of response	44.9125
Observations (or sum wgts.)	8

Table 7: Analysis of variance

Source	DF	Sum of squares	Mean square	F ratio
Model	3	27.90445	9.3015	0.2302
Error	4	161.65890	40.4147	Prob>F
C. Total	7	189.56335		0.8713

DISCUSSION

Pure drug had poor solubility of 0.35 mg/ml in PBS pH 6.8; whereas, PD-SD has significantly improved solubility of 29.64 mg/ml in PBS pH 6.8. This may be due to the effect of the carrier mannitol which was can be explained by configuration of areas containing elevated levels of dissolved mannitol at the surface of drug crystals in which the drug may be solubilized [7,8]. Hence, it will advance the consequent diffusion of ACV followed by dilution in the mass of the solution. As

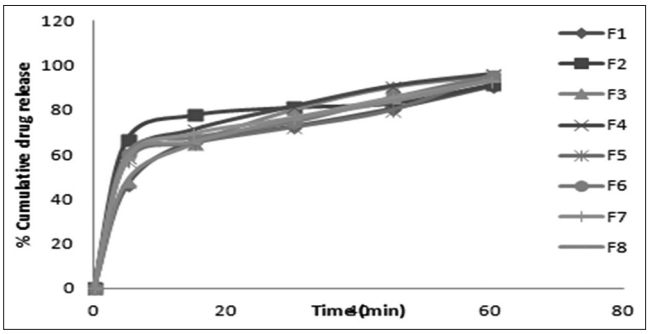

Fig. 3: *In vitro* release studies

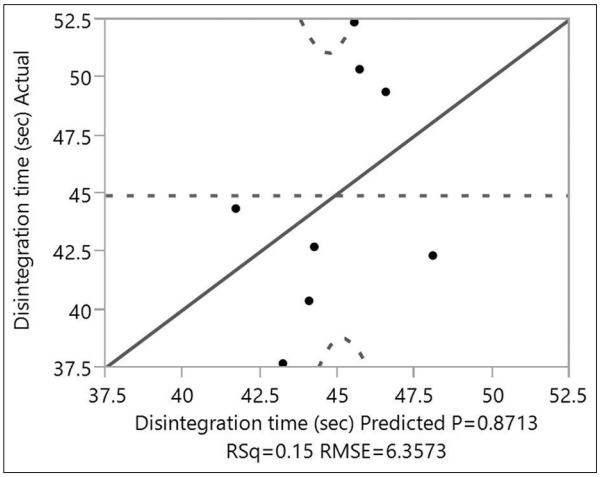

Fig. 4: Actual by predicted plot

Table 8: Parameter estimates

Term	Type	Estimate	Standard error	t ratio	p>|t|
Intercept	Biased	41.243333	10.48894	3.93	0.0171*
Drug (mg)	Zeroed	0	0		
HPMC 5 (mg)		0.00934	0.017981	0.52	0.6309
Glycerol (ml)		6	17.98104	0.33	0.7554
SSG (mg)		−0.166667	0.299684	−0.56	0.6078
Solvent (ml)	Zeroed	0	0		

HPMC: Hydroxypropyl methylcellulose, SSG: Sodium starch glycolate

Table 9: Sorted parameter estimates

Term	Type	Estimate	Standard error	t ratio	t ratio	p>|t|
SSG (mg)		−0.166667	0.299684	−0.56		0.6078
HPMC 5 (mg)		0.00934	0.017981	0.52		0.6309
Glycerol (ml)		6	17.98104	0.33		0.7554
Drug (mg)	Zeroed	0	0			
Solvent (ml)	Zeroed	0	0			

HPMC: Hydroxypropyl methylcellulose, SSG: Sodium starch glycolate

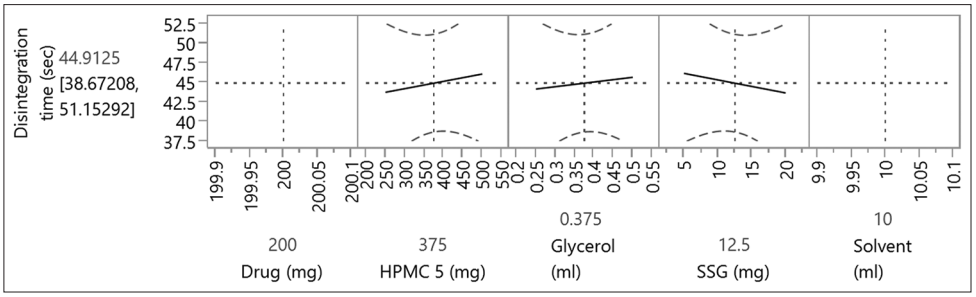

Fig. 5: Prediction profiler

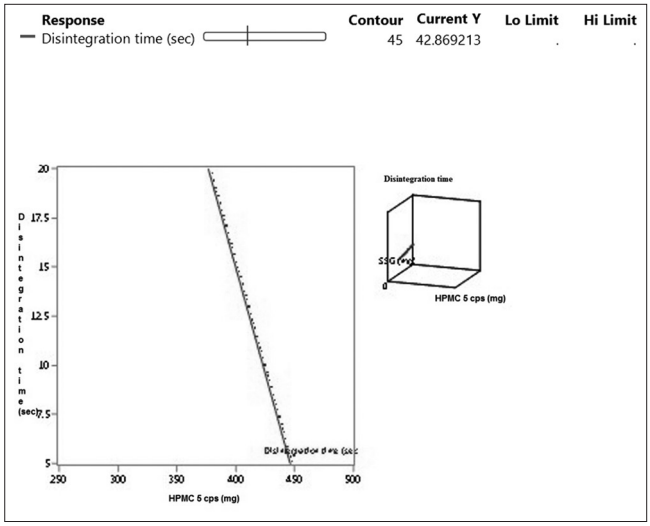

Fig. 6: Contour profiler

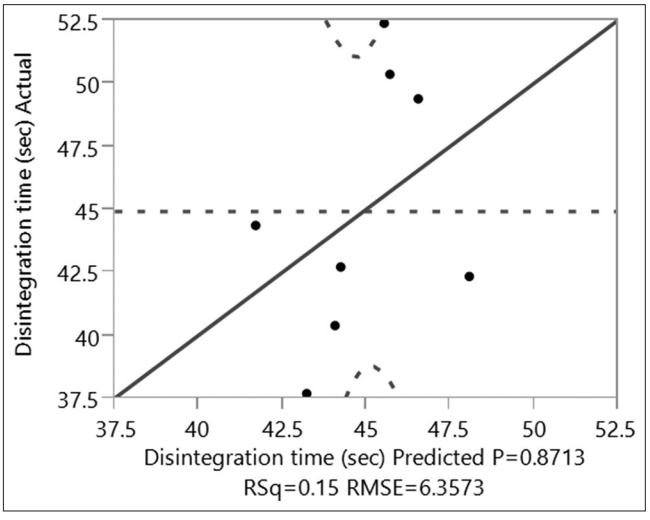

Fig. 7: Whole model actual by predicted plot

peaks of ACV were evident in the FTIR of mixture of ACV and other excipients, it proved that ACV was compatibility with the excipients. FTIR of pure drug ACV showed its characteristic major peaks (cm^{-1}) at 3524:OH stretching; 3439:NH_2 stretching; 3278:C-H aliphatic stretching; 1713:C=O stretching; and 778:C=H rocking. The FTIR spectra for drug-excipient compatibility study revealed no interaction between ACV and excipient (HPMC-5 and SSG) as evident by the main bands (cm^{-1}) of ACV at 3524:O-H overlapping; 3439:NH_2 stretching; 3278:C-H aliphatic stretching; 1713:C=O stretching; and 778:C=H rocking. Drug content for screening batches prepared was to be found lowest for F1 (87%±0.0084) and highest for F4 (95%±0.0123).

Whole model

Table 10: Summary of fit

R^2	
R^2 Adj	
Root mean square error	12.54209
Mean of response	44.9125
Observations (or sum wgts.)	8

Table 11: Analysis of variance

Source	DF	Sum of squares	Mean square	F ratio
Model	3	15540.104	5180.03	32.9301
Error	5	786.521	157.30	p>F
C. Total	8	16326.625		0.0010*

Tested against reduced model: Y=0

Table 12: Parameter estimates

Term	Estimate	Standard error	t ratio	p>|t|
HPMC 5 (mg)	0.0547918	0.027173	2.02	0.0998
Glycerol (ml)	51.451837	27.1729	1.89	0.1168
SSG (mg)	0.2541837	0.552248	0.46	0.6646

HPMC: Hydroxypropyl methylcellulose, SSG: Sodium starch glycolate

Table 13: Summary of fit

R^2	0.147204
R^2 Adj	−0.49239
Root mean square error	6.357258
Mean of response	44.9125
Observations (or sum wgts.)	8

Table 14: Analysis of variance

Source	DF	Sum of squares	Mean square	F ratio
Model	3	27.90445	9.3015	0.2302
Error	4	161.65890	40.4147	p>F
C. Total	7	189.56335		0.8713

Table 15: Parameter estimates

Term	Estimate	Standard error	t ratio	p>|t|
Intercept	41.243333	10.48894	3.93	0.0171*
HPMC 5 (mg)	0.00934	0.017981	0.52	0.6309
Glycerol (ml)	6	17.98104	0.33	0.7554
SSG (mg)	−0.166667	0.299684	−0.56	0.6078

HPMC: Hydroxypropyl methylcellulose, SSG: Sodium starch glycolate

Thickness of the formulations was found to be lowest for F2 (65.66 µm±2.08) and highest for F4 (95 µm±2). Folding endurance for film formulation was found to be lowest for F6 (83±2.160) and highest

Table 16: Results of the optimized formula

Drug content (%)±SD (n=3)	Thickness (μm)±SD (n=3)	Surface pH±SD (n=3)	Folding endurance±SD (n=3)	Disintegration time (s) Predicted	Disintegration time (s) Actual±SD(n=3)
97.13±0.0044	90±1.632	7.46±0.133	103±6.23	42.86	43±1.632

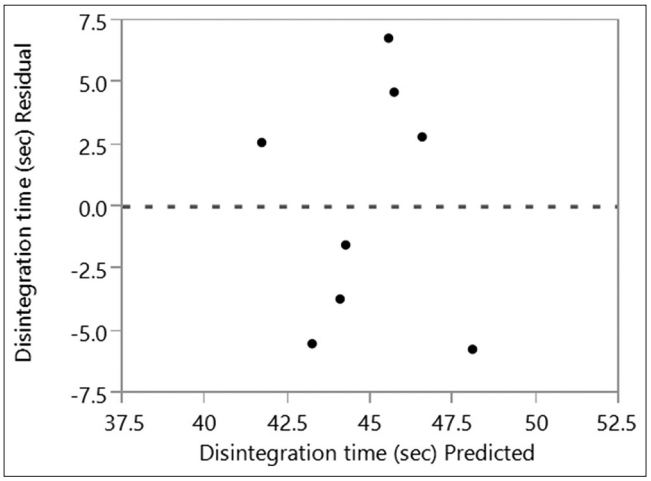

Fig. 8: Residual by predicted plot

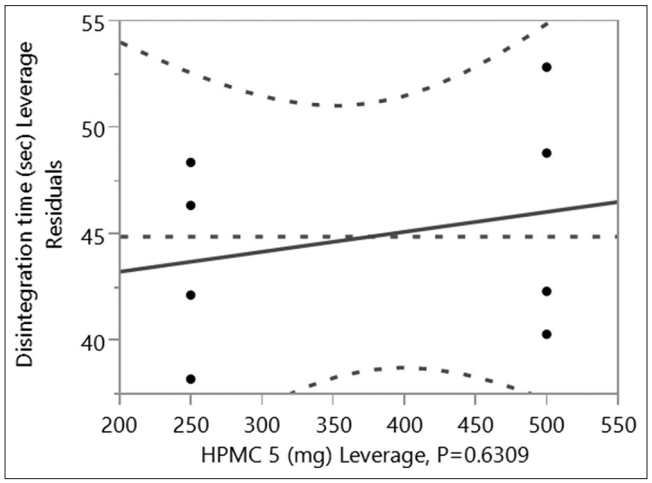

Fig. 9: Hydroxypropyl methylcellulose 5 (mg) leverage plot

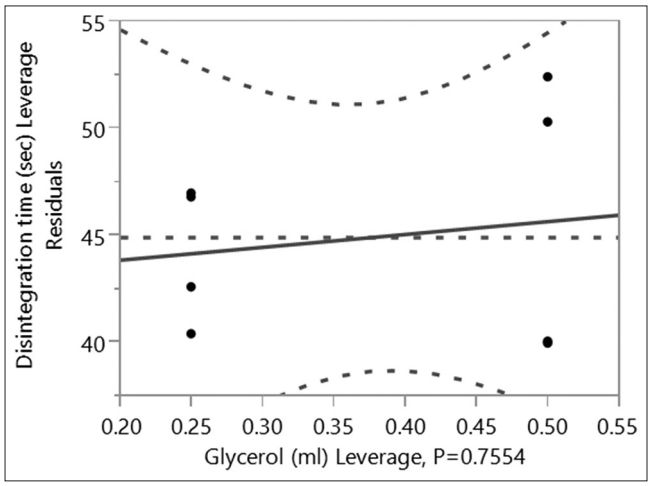

Fig. 10: Glycerol (ml) leverage plot

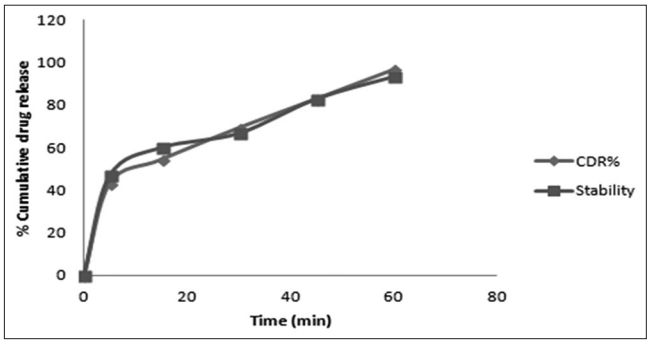

Fig. 11: *In vitro* release profile of the optimized formula before and after short-term accelerated stability study

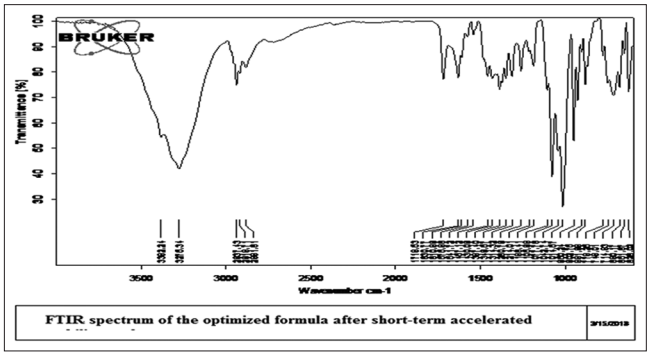

Fig. 12: Fourier transform-infrared spectrum of the optimized formula after short-term accelerated stability study

for F4 (100±4.08). Disintegration time was found to be lowest for F4 (37.66±2 s) and highest for F8 (52±2 s). Surface pH was found to be lowest for F1 (7.07±0.0309) and highest for F4 (7.466±0.36). Percentage CDR of screening batches was found to be lowest for F1 (46.04%±0.00124) and highest for F4 (96.12%±0.00124). Drug content for optimized formulation was found to be 97.13% ±0.0044. Percentage CDR was found to be 96.89%±0.0033 may be due to rapid uptake of water, followed by rapid and enormous swelling of SSG. Thickness of film formulation was found to be 90 μm±1.639 and folding endurance was found to be 103.33±6.23. Surface pH of film formulation was found to be 7.46±0.133 and disintegration time of films formulation was found to be 43±1.6329 s (predicted: 42.8 s). Thus, the actual value of the disintegration time was in close agreement with the predicted value. Post short-term accelerated stability studies showed that ACV remained stable as evident by the peaks shown in the FTIR (Fig. 5); also, the percentage CDR was recorded at 93.36% which was close to the original value of 96.12%.

CONCLUSION

As the solubility profile of ACV-SD showed an improvement, it was concluded that such ACV-SD could be beneficial in enhancement of dissolution and consequently the oral bioavailability of ACV. The optimized oral films of ACV-SD were rapidly disintegrating indicating the success of this research work. Future scope of the study would be to study its effectiveness and safety in animals and humans followed by scale-up.

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AUTHOR'S CONTRIBUTION

Both the authors have equally contributed toward the research and research article.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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