FORMULATION, IN-VITRO EVALUATION, AND OPTIMIZATION OF ACYCLOVIR TABLET–IN–TABLET OF OUTER IMMEDIATE RELEASE AND INNER SUSTAINED RELEASE (FLOATING TABLET)

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Abstract

Acyclovir is an antiviral drug widely used for the treatment of various viral infections, including herpes simplex and varicella-zoster viruses. However, its short half-life and frequent dosing regimen pose challenges in maintaining consistent therapeutic levels. To overcome these limitations, this study aimed to develop a novel Acyclovir tablet with an innovative design of an outer immediate-release layer and an inner sustained-release layer utilizing a floating tablet approach. The formulation process involved selecting appropriate excipients, optimizing drug loading, and establishing suitable manufacturing techniques. The immediate-release layer was designed to provide an initial burst of Acyclovir for immediate therapeutic effect, while the sustained-release layer was intended to maintain a prolonged release profile, ensuring a sustained drug release over an extended period. In-vitro evaluation of the developed Acyclovir tablet included various tests, such as weight variation, hardness, and friability, disintegration, and drug release studies. These evaluations were performed to assess the tablet's physicochemical characteristics, mechanical strength, disintegration time, and drug release profiles. The optimized Acyclovir tablet demonstrated desirable properties, including acceptable physical parameters and consistent drug release kinetics. The immediate-release layer exhibited a rapid drug release within the first hour, mimicking the initial therapeutic requirement, while the sustained-release layer maintained a steady release over an extended period, ensuring a prolonged therapeutic effect. The floating tablet design allowed the sustained-release layer to remain buoyant, promoting gastric retention and enhancing drug absorption. Overall, the developed Acyclovir tablet with an outer immediate-release and inner sustained-release (floating tablet) provides a promising approach for achieving optimized drug delivery characteristics. This innovative formulation has the potential to enhance patient compliance by reducing the frequency of dosing while maintaining effective therapeutic levels. Further in-vivo studies and clinical trials are warranted to validate the tablet's performance, evaluate its pharmacokinetics, and assess its therapeutic efficacy for the treatment of viral infections.

Keywords: Acyclovir, HPMC K-4 M, HPMC K-15M, HPMC K-100 M, Sodium Carbonate, Sodium alginate

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INTRODUCTION

Acyclovir is a widely used antiviral medication primarily prescribed for the treatment of infections caused by herpes simplex virus (HSV) and varicella-zoster virus (VZV). To enhance its therapeutic efficacy and patient compliance, researchers have developed a novel formulation approach involving the design of an Acyclovir tablet with a unique composition and release profile. This tablet comprises an outer immediate-release layer and an inner sustained-release (floating) layer, collectively known as the "Tablet -In-Tablet" system.[1-3]

The formulation of the Acyclovir In-Tablet involves careful selection and combination of excipients to achieve the desired drug release characteristics. The outer immediate-release layer aims to provide a rapid initial release of the drug, ensuring its quick absorption and onset of action. It typically contains rapidly disintegrating and/or fast-dissolving excipients, such as super disintegrants, to facilitate the disintegration and dissolution of the tablet upon ingestion. By doing so, the outer layer enables the immediate availability of the drug for systemic circulation.[4]

The inner sustained-release layer, on the other hand, is designed to provide a controlled and prolonged release of Acyclovir over an extended period. The key feature of this layer is its ability to float in the gastric fluid, thereby prolonging the residence time of the tablet in the stomach. This floating characteristic is achieved by incorporating gas-generating agents or hydrocolloids into the formulation, which create a buoyant effect upon contact with gastric fluid. As a result, the tablet remains buoyant on the surface of the gastric fluid, allowing for sustained drug release and improved bioavailability.[5-8]

The in-vitro evaluation of the Acyclovir In-Tablet involves a series of tests to assess its performance and release kinetics. Dissolution studies are conducted using appropriate dissolution apparatus to measure the drug release profiles from both the immediate-release and sustained-release layers. Various dissolution media, such as simulated gastric fluid (SGF) and simulated intestinal fluid (SIF), may be employed to mimic the gastrointestinal conditions. The collected samples are analyzed using validated analytical methods to quantify the drug concentration at specific time intervals. [9-11]

Optimization of the Acyclovir In-Tablet formulation is crucial to achieve the desired drug release profile, bioavailability, and therapeutic efficacy. It involves the systematic variation of formulation components, such as excipients, drug loading, and layering techniques, to optimize the release kinetics and floating behaviour of the tablet. Design of Experiments (DoE) approaches, such as factorial design or response surface methodology, can be employed to efficiently explore and optimize the formulation space. By evaluating and comparing the results of in-vitro dissolution studies, the formulation can be refined to achieve the desired release pattern, such as a rapid initial release followed by sustained release. [12-15]

In conclusion, the development of the Acyclovir tablet with an In-Tablet system, consisting of an outer immediate-release layer and an inner sustained-release (floating) layer, represents an innovative formulation approach. This design aims to enhance the therapeutic efficacy and patient compliance of Acyclovir by providing both an immediate release and a prolonged drug release profile. Through rigorous in-vitro evaluation and optimization, the formulation can be tailored to achieve the desired drug release characteristics, ensuring effective treatment of HSV and VZV infections.[16

Material and Method:

Acyclovir were gift sample from Alkem Pharmaceutical, Mumbai.

Also Sodium Bicarbonate, Sodium alginate, Magnesium stearate, Talc were purchased from SD Fine Chem, Boisar, and Maharashtra. All other chemicals used were of analytical reagent grade.

1. Formulation of monolayer sustained release tablet [17]

HPMC grades are exclusively designed hydrophilic matrix agent, suitable for direct compression. HPMC 90SH SR grades have characteristic of quick hydration and gel formation. The selection of HPMC grades affects the initial wetting, swelling, hydration and gel strength. Low density of HPMC along with its SR properties makes it suitable candidate for floating sustained release drug delivery system.

Ingredients	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**
Acyclovir	200	200	200	200	200	200	200	200	200
HPMC K4 M	40	60	80	-	-	-	-	-	-
HPMC K15 M	-	-	-	40	60	80	-	-	-
HPMC K100 M	-	-	-	-	-	-	40	60	80
Sodium bicarbonate	20	20	20	20	20	20	20	20	20
Gelatin	60	60	60	60	60	60	60	60	60
Lactose	68	48	28	68	48	28	68	48	28
Talc	4	4	4	4	4	4	4	4	4
Mg stearate	8	8	8	8	8	8	8	8	8
Color	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total Weight	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**

Table no. 1*:* Formulation of monolayer sustained release tablet

2) Formulation of immediate release tablet [18]

Table no. 2: Composition of monolayer immediate release tablets (all weight in mg)

Ingredients	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**
Acyclovir	200	200	200	200	200	200	200	200	200
Cross carmellose sodium	50	75	100	-	-	-	25	37.5	50
Sodium starch glycolate	-	-	-	50	75	100	25	37.5	50
Starch	75	75	75	75	75	75	75	75	75
Lactose	160	135	110	160	135	110	160	135	110
Talc	5	5	5	5	5	5	5	5	5
MG stearate	10	10	10	10	10	10	10	10	10
Total weight	500	500	500	500	500	500	500	500	500

The main use of Cross caremellose Sodium is in tablet formulations as a disintegrant and Lactose as diluent. Although CCS is insoluble in water, it is an effective tablet disintegrant as it swells to several times of its original bulk on contact with water. Concentrations up to 10% w/w may be used in tablet formulations; above this concentration the tablet hardness is reduced. Here we used it as a disintegrant.

3. Formulation of tablet in tablet [19]

Formulation of sustained release layer with HPMC different grades

Better control on drug release rate is possible by using tablet in tablet formulation. Immediate release layer was designed to assist in achieving initial release of drug, whereas sustained release layer of HPMC was designed to assist in prolonging drug release over period of time.

Table No. 3: Formulation of Tablet in Tablet

	Ingredients	**Batches**								
		A1	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**
IR	Acyclovir	200	200	200	200	200	200	200	200	200
	Croscarmellose sodium	50	75	100	-	-	-	25	37.5	50
	Sodium starch glycolate	-	-	-	50	75	100	25	37.5	50
	Starch	75	75	75	75	75	75	75	75	75

	Lactose	160	135	110	160	135	110	160	135	110
	Talc	5	5	5	5	5	5	5	5	5
	Mg. Stearate	10	10	10	10	10	10	10	10	10
	Wt of IR layer	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**
		S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**
SR	Acyclovir	200	200	200	200	200	200	200	200	200
	HPMC K4M SR	40	60	80	-	-	-	-	-	-
	HPMC K15M SR	-	-	-	40	60	80	-	-	-
	HPMC K100MSR	-	-	-	-	-	-	40	60	80
	Sodium bicarbonate	20	20	20	20	20	20	20	20	20
	Gelatin	60	60	60	60	60	60	60	60	60
	Lactose	68	48	28	68	48	28	68	48	28
	Talc	4	4	4	4	4	4	4	4	4
	Mg. stearate	8	8	8	8	8	8	8	8	8
	Colour	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Wt of SR layer	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**
	Total weight	**900**	**900**	**900**	**900**	**900**	**900**	**900**	**900**	**900**

*****All weights are in mg.

FORMULATION AND EVALUATION MONOLAYER SUSTAINED RELEASE TABLETS

Compression parameters of monolayer SR tablet

Sr. No.	**Parameters**	**Batches**								
		S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**
1	Density (g/ml)	1.181	1.1607	1.1483	1.1535	1.1561	1.1575	1.1321	1.1445	1.1481
2	Floating lag time (sec)	10	10	12	11	13	12	13	14	15
3	Duration of floating (hr)	<11	<11	>11	>11	>11	>11	<11	<11	<11
4	Hardness (kg/cm^2)	4-4.5	4-4.5	4-4.5	4-4.5	4-4.5	4-4.5	4-4.5	4-4.5	4-4.5
5	Friability (%)	0.45	0.41	0.41	0.34	0.46	0.45	0.35	0.42	0.37
6	Weight of tablet (mg ± S.D.)	375.2 ±5	380.4 ± 5	379.1 ±5	310.2 ± 5	415.3 ± 5	412.2 ± 5	380.5 ± 5	390.6 ±5	392.4 ± 5
7	Assay (% ± S.D.)	98.10 ±2.10	98.89 ± 2.91	99.20 ± 1.52	99.56 ± 1.88	98.19 ± 1.31	97.25 ± 2.51	96.45 ± 2.41	98.92 ± 2.47	97.92 ±2.47

Table No. 4 : *Evaluation of post compression parameters of monolayer tablets (Batch S1 to S9)*

Dissolution profile:

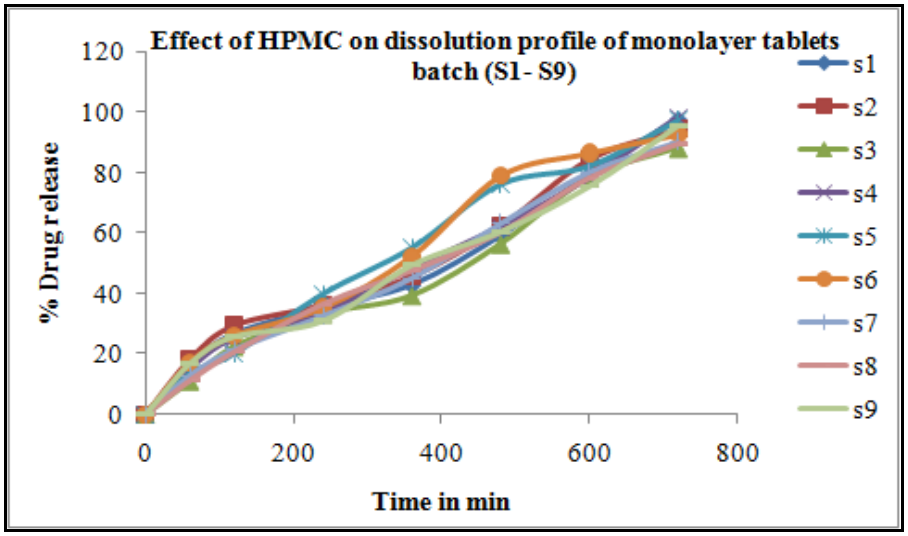

Figure No. 2:*Effect of HPMC on dissolution profile of monolayer tablets batches (S1-S9)*

IMMEDIATE RELEASE (IR) TABLETS

Compression parameters of IR tablets powder blend

Sr. No	Parameters	Batches								
		I1	I2	I3	I4	I5	I6	I7	I8	I9
1	Density (g/ml)	1.147	1.132	1.142	1.151	1.136	1.146	1.169	1.152	1.159
2	Wetting time (sec)	210 ± 11	206 ± 10	204 ± 13	155 ± 8	150 ± 18	152 ± 13	60 ± 5	65 ± 2.5	69 ± 1.2
3	Disintegration time (min)	5.0 ± 0.20	5.0 ± 0.21	5.0 ± 0.25	2.58 ± 0.17	2.45 ± 0.78	2.40 ± 0.65	0.5 ± 0.07	0.49 ±0.06	0.48± 0.05
4	Weight of tablet (mg ± S.D)	494 ± 2.87	483 ± 1.45	502 ± 1.32	505±2.32	518± 1.25	523 ± 1.25	502 ± 2.32	478± 1.06	489 ± 1.30
5	Assay (% ± S.D.)	98.64 ± 1.23	98.54±1.61	98.21 ± 1.45	99.25±1.09	98.25 ± 1.40	98.56 ± 1.25	98.54 ±1.61	98.45 ± 0.15	98.55 ± 0.52

Table No. 5: *Evaluation of compression parameters of tablets (Batch I1 to I9)*

Dissolution profile

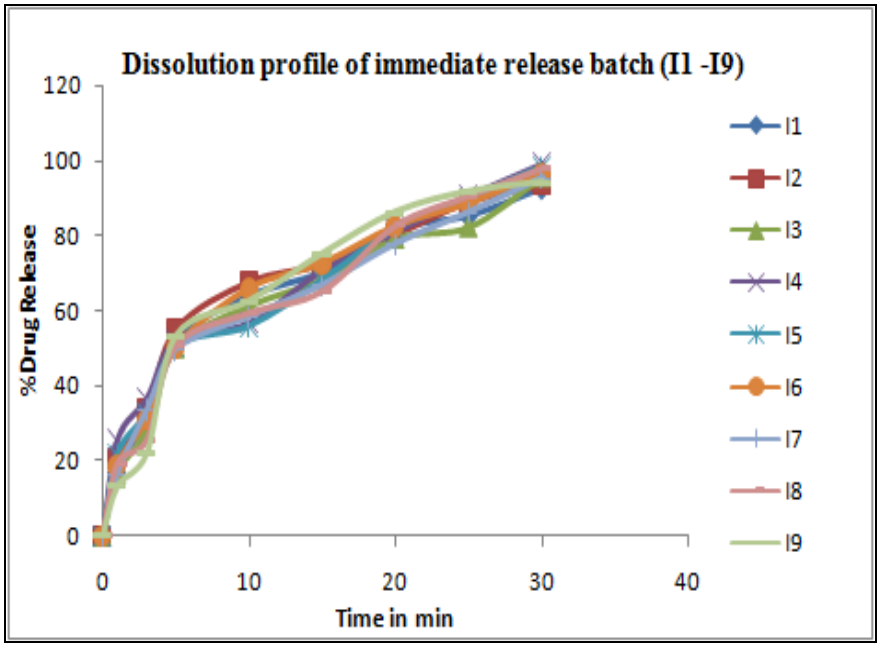

Figure No. 3: *Dissolution profile of immediate release tablets batches (I1-I9)*

TABLET IN TABLETS

Compression parameters of tablet in tablet:

Sr. No.	Parameters	Batches								
		1	2	3	4	5	6	7	8	9
1	Density (g/ml)	1.1661	1.1223	1.1792	1.1169	1.1201	1.1550	1.1303	1.0935	1.132
2	Floating lag time (sec)	11	13	16	10	15	11	14	12	11
3	Duration of floating (hr)	<11	<11	<11	>11	>11	>11	<11	<11	<11
4	Hardness (kg/cm^2)	4-4.5	4-4.5	4-4.5	4-4.5	4-4.5	4-4.5	4-4.5	4-4.5	4-4.5
5	Friability (%)	0.42	0.51	0.49	0.46	0.53	0.64	0.83	0.35	0.78
6	Weight of tablet (mg ± S.D.)	862.2 ± 2.3	881.1 ± 2.5	894.4 ± 2.7	898.4 ± 2.4	904.3 ± 2.4	913.2 ± 2.3	938.5 ± 2.1	890.3 ± 3.1	941.1 ± 1.8
7	Assay (% ± S.D.)	98.19 ± 2.11	100.21 ±1.98	98.74 ± 2.87	99.34 ± 2.87	99.76 ± 1.84	98.27 ± 2.01	98.73 ± 2.96	99.39 ± 2.43	99.99 ± 2.81

Table No. 6 : *Evaluation of post compression parameters of tablet in tablets formulated with HPMC (Batch-1 to 9)*

Dissolution profile

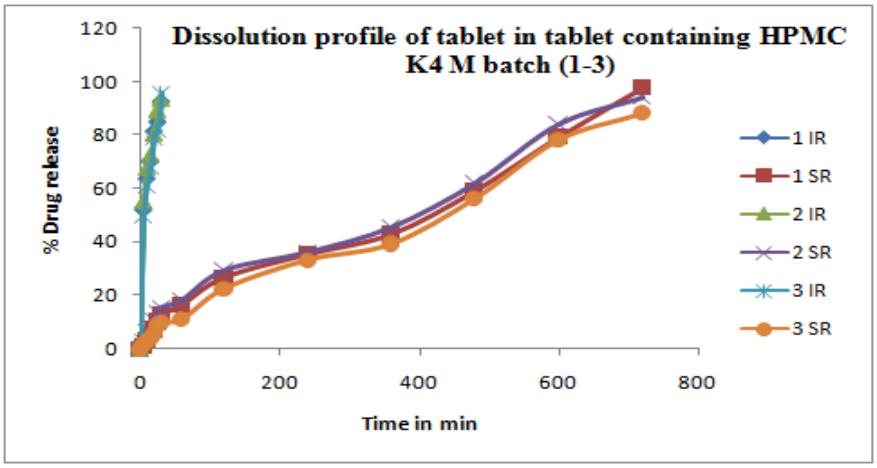

Figure No. 4: *Dissolution profile of tablet in tablet containing HPMC K4 M batches (1 -3)*

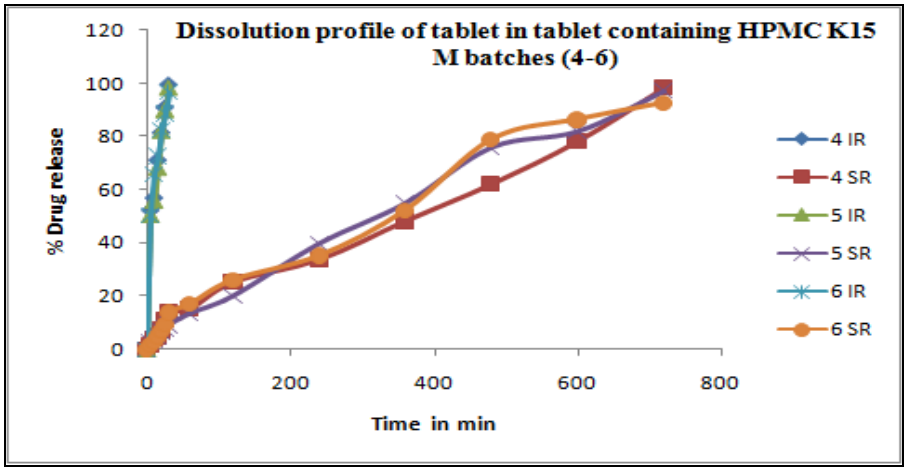

Figure no. 5 : *Dissolution profile of tablet in tablet containing HPMC K15 M batches (4 -6)*

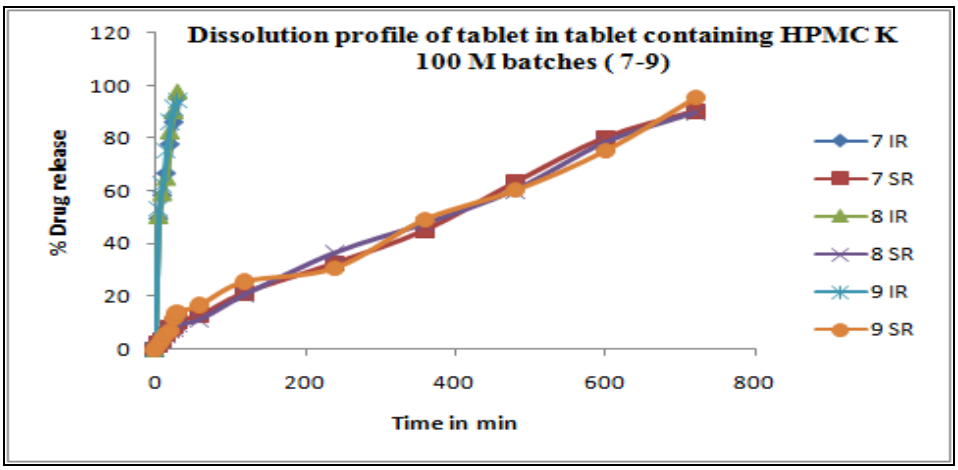

Figure no. 6: *Dissolution profile of tablet in tablet containing HPMC K100 M batches (7-9)*

Dissolution data treatment

Table No. 7: *Statistics of dissolution data treatment*

Batches	Zero order	First order	Higuchi model	K-P model		Comparison of dissolution profile	
	R^2	R^2	R^2	R^2	N	f_2	f_1
Monolayer of tablet (SR)							
S1	0.931	0.997	0.989	0.989	0.528	52	15
S2	0.921	0.986	0.974	0.962	0.521	50	12
S3	0.865	0.956	0.954	0.972	0.596	56	11
S4	0.904	0.994	0.974	0.981	0.570	48	10
S5	0.895	0.985	0.965	0.997	0.590	35	14
S6	0.871	0.978	0.955	0.981	0.675	56	11
S7	0.920	0.998	0.984	0.985	0.619	49	18
S8	0.939	0.995	0.979	0.964	0.599	42	11
S9	0.940	0.996	0.988	0.922	0.602	41	25
Monolayer of tablet (IR)							
I1	0.667	0.807	0.775	0.780	0.222	49	17
I2	0.785	0.815	0.782	0.856	0.256	45	16
I3	0.869	0.945	0.845	0.865	0.296	25	10
I4	0.887	0.976	0.956	0.980	0.326	48	18
I5	0.956	0.965	0.932	0.975	0.456	55	11
I6	0.985	0.975	0.921	0.961	0.421	45	12
I7	0.810	0.991	0.900	0.949	0.247	62	10
I8	0.789	0.920	0.891	0.923	0.352	51	36
I9	0.845	0.952	0.899	0.965	0.456	50	25
Tablet in Tablet							
1	0.957	0.971	0.987	0.993	0.279	49	16
2	0.982	0.965	0.975	0.989	0.358	45	11
3	0.857	0.985	0.965	0.992	0.458	32	22
4	0.916	0.983	0.987	0.994	0.297	55	8
5	0.885	0.995	0.975	0.985	0.356	44	10
6	0.931	0.965	0.998	0.858	0.520	39	17
7	0.972	0.970	0.957	0.962	0.300	46	22
8	0.985	0.952	0.921	0.982	0.452	42	20
9	0.859	0.945	0.911	0.956	0.545	45	11

RESULT AND DISCUSSION

Monolayer tablets of Acyclovir were not found to be useful in achieving the desired release profile. Whereas SR and IR tablet in tablet batches were found to be useful in achieving initial burst release. HPMC alone is not sufficient to give desired floating properties to tablet, whereas HPMC along with gas generating agent sodium bicarbonate gives tablets having desired floating properties. Cross caremelose sodium and SSG used in immediate release enhances the disintegration property of tablet. Different grade of HPMC polymer are incorporated and HPMC K15 which is included in batch 4 to 6 gives satisfactory result.

Presence of Talc and mg. Stearate enhances the flow property of granules used in tablet preparation. By considering overall results of batches we can conclude that tablets formulated with mixture of HPMC K15M SR are good for once a day dosage form of acyclovir tablet in tablet dosage form. As batch 4 is optimized batch it undergoes under in vivo study giving satisfactory results for the same.

SUMMARY AND CONCLUSION

Using tablet-in-tablet technology for preparation of the acyclovir is done by considering the advantages for tablet-in-tablet technique like, the tablet in tablet technique provides initial drug release to provide rapid onset of action followed by a period of sustained release in quick or slow system. It reduces dosing frequency, this system allows loading of higher amount of drug. It improves patient compliance and mostly importantly the combination of immediate release and delayed or sustained release dosage form can formulate in single tablet.

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