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FORMULATION AND EVALUATION OF TABLET-IN-TABLET FOR INNER TABLET ACYCLOVIR AS SUSTAINED RELEASE AND OUTER TABLET PARACETAMOL AS IMMEDIATE RELEASE FOR CHICKENPOX TREATMENT

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ABSTRACT

Today all the world allopathic system of medicine dominates the "Traditional medicine and healing art" due to its strong link with modern sciences & Technology. Better appreciation and integration of pharmacokinetic and pharmacodynamics principles in the design of drug delivery system has been developed a lead to improve therapeutic efficiency. Drug research has evolved and matured through phases beginning from pill to pharmaceutical dosage form. In this we can study Tablet in Tablet design "Tablet-in-Tablet"expression. Tablet presses allowing such a technique known as aletnate tablet presses, tablet-in-tablet" presses, or dry coat tablet presses and are known as art.

INTRODUCTION

Drug therapy has a profound influence on the health statistics all over the world. The effective and rational use of the drug constitutes one of the most important of the health programmer. Today all the world allopathic system of medicine dominates the "Traditional medicine and healing art" due to its strong link with modern sciences & Technology. Better appreciation and integration of pharmacokinetic and pharmacodynamics principles in the design of drug delivery system has been developed a lead to improve therapeutic efficiency. Drug research has evolved and matured through

phases beginning from pill to pharmaceutical dosage form.

Tablet in tablet:- A "Tablet-in-Tablet" degign means that the dosage form comprises an inner tablet that is covered ans surrounded by an outercoat, which is compressesd onto he inner tablet. Both inner and outer tablet are made by a compression process that is characteristic for making tablets, hence the "Tablet-in-Tablet"expression. Tablet presses allowing such a technique known as alternate tablet presses, tablet-in-tablet" presses, or dry coat tablet presses and are known as art.

The inner tablet and the outer tablet are normally the same shape, preferably round including fat round or a convex round shaped. The inner tablet usually has a diameter of 7 mm or less usually 6 mm or less. The outer tablet has a diameter of about 11 mm or less , typically 9 to 10.5 millimetres and in some embodiments about 10 millimeters.

AIM AND OBJECTIVE

- The intention of this formulation is better therapeutic efficiency by controlling drug release
- The objective of the study was to develop Tablet-in-Tablet tablet of Acyclovir and Paracetamol for rew
- To minimize frequency of administration.
- To study pre-formulation properties like Melting Point, Solubility of drug.
- To investigate the drug-excipient interaction studies using FT-IR and DSC.
- To prepare tablet with desired release pattern and to avoid degradation of drug.
- Compare the different formulations' release profiles
- To evaluate the formulation with respect to various physical parameters: Hardness, weight variation, thickness and drug content.
- To improve physiological and pharmacological response.
- To study stability study of the optimize formulation as per ICH guidelines.

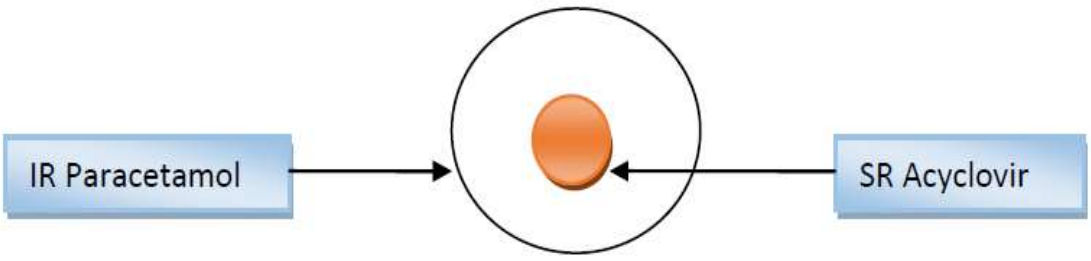


Fig. 1: Tablet-in-Tablet dosage form.

Scope

- In-vivo study for optimized formulation.
- Other polymer (HPMC K15M, HPMC K4M) can be used for design formulation.

Experimenta work

Preformulation study

Preformulation is primary step in the rational development of dosage form of a drug substance. Prior to formulation, it may be described as a research of the physical and chemical characteristics of the drug material both on its own and when mixed with excipients. Pre-formulation testing's main goal is to produce data that the formulator can utilize to create a stable, bioavailable dosage form that can be manufactured. The goals of the program therefore are;

- To determine essential physiochemical properties of novel medicinal compounds
- To determine its kinetics rate profile.
- To establish its compatibility with different excipients.

Characterization of drug

Description: Color, Appearance and odour. The sample was observed visually.

Determination of melting point

Melting point of drugs was determined by using glass capillary method. Make-Veego programmable melting point apparatus was used. The silicon bath in which the capillary holding the medication was put was heated uniformly by taking the necessary measures.

Solubility studies

Solubility of drugs was determined by using various solvents.

The solubility of Paracetamol was determined in distill water methanol, acetone, chloroform. The solubility of Acyclovir was determined in distill water, methanol.

UV-Spectroscopic scanning -spectral analysis

Determination of λmax of Paracetamol[89]

Paracetamol 10 mg was accurately weighed and stock solution (100µg/ml) was prepared.The stock solution was further diluted using methanol to get serial dilutions.A dilution was kept in in cuvette. The UV spectrum was recorded using double beam UV-visible spectrophotometer

in the range of 200nm-400nmwaveleng.

Preparation of standard curve

A stock solution of Paracetamol (100µg/ml) was prepared by dissolving 10mg of drug in distill water and final volume was made to 100ml. The solutions in concentration range of 2-10µg/ml were prepared by appropriate dilutions of stock solutions. The UV absorbance of these solutions was determined spectrophotometricaly at λmax 243nm.

***Determination of λmax of acyclovir*[90]**

Acyclovir (10mg) was accurately weighed and 100µg/ml stock solution was prepared. The stock solution was further diluted using by using distlled water to get dilutions.The UV spectrum was recorded using double beam UV-visible spectrophotometer in the range of 200-400nmwavelength.

Preparation of standard curve

A stock solution of Acyclovir l was prepared by dissolving 10mg of Acyclovir in distill water and final volume was made to 100ml. The solutions in concentration range of 5-25µg/ml were prepared by appropriate dilutions of stock solution.The UV absorbance of thesesolutions was determined spectrophotometrically at λmax 253nm.

Drug-excipients compatibility study

***Differential scanning calorimetry*[45]**

Table 1: Formulation of sustained release layer.

Sr. No	Ingredients	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8	SR9
1.	Acyclovir	20	20	20	20	20	20	20	20	20
2.	Gelatin	15	15	15	15	15	15	15	15	15
3.	Dicalcium Phosphate	47	42	37	47	42	37	47	42	37
4.	HPMC K4M	15	20	25	-	-	-	7.5	10	12.5
5.	HPMC K15M	-	-	-	15	20	25	7.5	10	12.5
6.	Color (Amaranth)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
7.	Mg Sterate	1	1	1	1	1	1	1	1	1
8	Talc	2	2	2	2	2	2	2	2	2
9	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Total (mg)	100	100	100	100	100	100	100	100	100

***** All quantities are in mg

Thermo gram was recorded on Ta instruments/Q 20 model. DSC thermo grams of Paracetamol, Acyclovir, mixture of Paracetamo and excipentsl, Acyclovir and excipients. The drug exhibited a sharp melting endotherm at 172°C, 258°C respectively. No change in

the endotherm of the drugs was observed in the mixture, which indicates no interaction betweenthe excipients and drugs.

Table 2: Formulation of immediate release layer.

Sr. No.	Ingredients	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8	IR9
1.	Paracetamol	120	120	120	120	120	120	120	120	120
2.	Croscarmellose sodium	90	120	150	-	-	-	45	60	75
3.	Sodium Starch Glycolate	-	-	-	90	120	150	45	60	75
4.	Microcrystalline cellulose	282	252	222	282	252	222	282	252	222
5.	Starch	90	90	90	90	90	90	90	90	90
6.	Talc	12	12	12	12	12	12	12	12	12
7.	Aerosil	6	6	6	6	6	6	6	6	6
8.	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Total (mg)	600	600	600	600	600	600	600	600	600

** All quantities are in mg*

Preparation of granules

Preparation of sustained release granules of acyclovir

- Granulation done by wet granulation method.
- Weigh all the ingredients and pass through #60 mesh.
- Mixed all ingredients except lubricant and add binder solution of gelatin and formed uniform dough mass and pass through # 8 mesh.
- Dried granules at 60°C in hot air oven for 15 minutes.
- The dried granules were then sieved with #16 mesh.
- Then Added Mg streate and Talc and mixed for 2 min
- Then compressed into tablet.

Preparation of immediate release granules of paracetamol

- Granulation done by wet granulation method.
- Weigh all the ingredients and pass through #60 mesh
- Mixed all ingredients except lubricant and add binder solution of Starch and formed uniform dough mass and pass through #8 mesh
- Dried granules at 60
- C in hot air oven for 15 minutes.
- The dried granules were then sieved with #16 mesh.

- Added Talc and Aerosil and mixed for 2 min
- Then compressed into tablet.

Fig. 1: Tablet in tablet.

RESULTS AND DISCUSSION

1. UV-Visible Spectroscopic scanning-spectral analysis

Determination of UV Absorbance Maxima of Paracetamol

Suitable analytical method was developed for using UV spectroscopy and analytical wavelength of λmax 243nm was identified in Distill water. Calibration curves were constructed in these media. The R2 value were 0.996 for distill waterl solution. Beer Lambert law obeyed in the range of 0-25µg/ml.

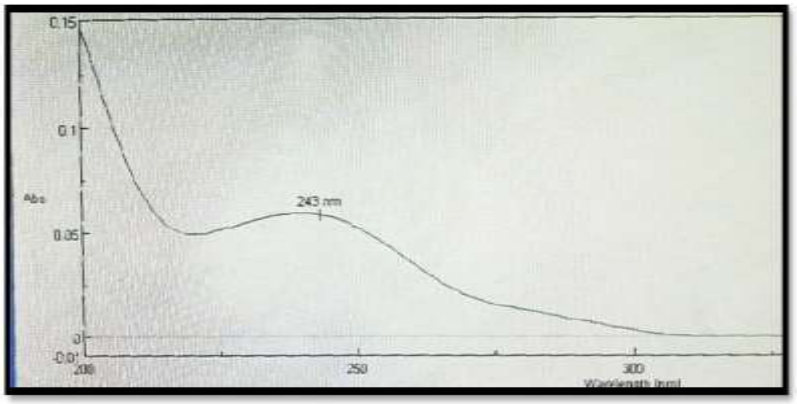


Fig. No. 2: Wavelength maxima of paracetamol in distill water.

Standard calibration curve

Standard calibration curve was plotted is an absorbance Vs concentration in Dt Waterl

solution. Absorbance value is plotted in Table. The beer's range of the Parcaetamol obeyed was 0-25 µg/ml.

Table 3: Standard calibration curve data for paracetamol in distill water.

Sr. No	Conc. (µg/ml)	Abs. at (243nm)
1.	0	0
2.	5	0.1986
3.	10	0.3898
4.	15	0.5789
5.	20	0.7568
6.	25	0.9686

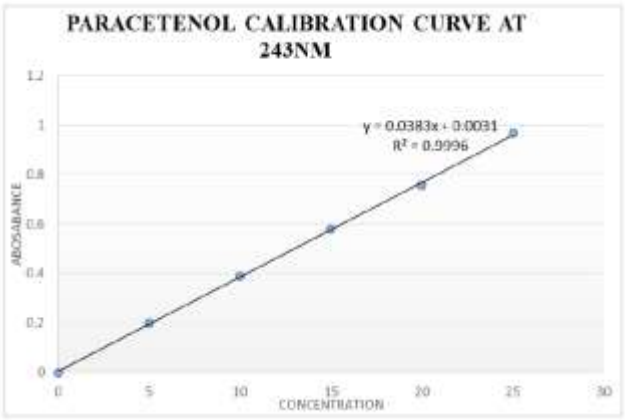


Figure 3: Calibration curve of Paracetamol in Distill water (Linearity of paracetamol).

2. Determination of UV Absorbance Maxima of Acyclovir

Suitable analytical method was developed for Acyclovir using UV spectroscopy and analytical wavelength of λmax 253 nm was identified in distill water. Calibration curves were constructed in these media. The R^2 value were 0.9996. Beer Lambert law obeyed in the range of 0-25µg/ml

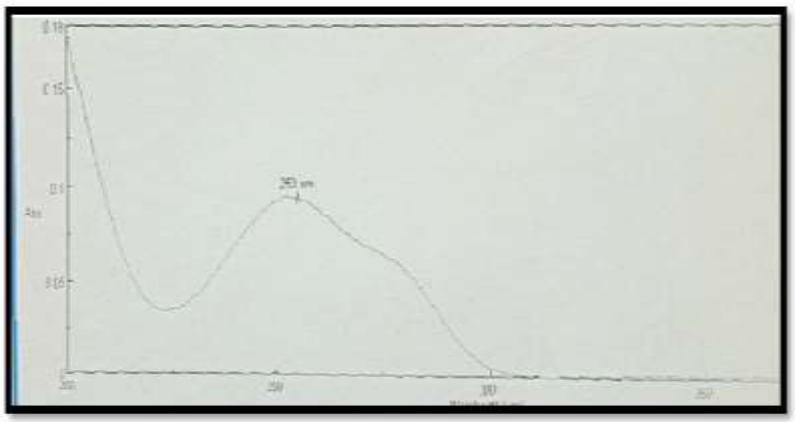


Fig. 4: Wavelength maxima of acyclovir in distill water.

Standard calibration curve

Standard calibration curve was plotted is an absorbance Vs concentration in Distill Water solution. Absorbance value is plotted in Table. The beer's range of the Acyclovir obeyed was 0-25 µg/ml.

Table 4: Standard calibration curve data for acyclovir in distill water.

Sr. No.	Conc. (µg/ml)	Abs. at (253nm)
1.	0	0
2.	5	0.1898
3.	10	0.3968
4.	15	0.5898
5.	20	0.7685
6.	25	0.9789

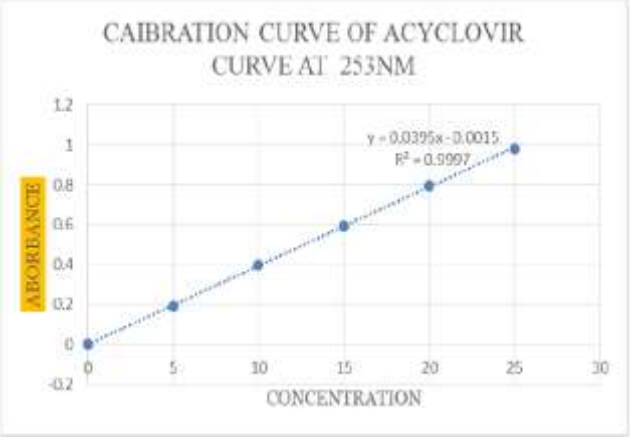


Figure 5: Calibration curve of acyclovir in distill water (Linearity of acyclovir).

Drug-excipient compatibility studies

Differential Scanning Calorimetry (DSC) study

DSC thermo grams of Paracetamol, Acyclovir and Exciepent mixture of are depicted in Fig. The drug exhibited a shsarp melting endotherm at 172°C, 258°C respectively. No change in the endotherm of the drug was observed in the mixture, which indicates the absece of any interaction between the drug and excipient.

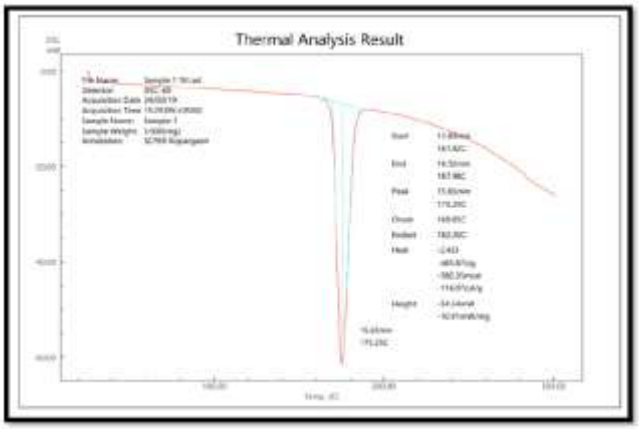


Fig. 6: DSC Thermogram of API Paracetamol.

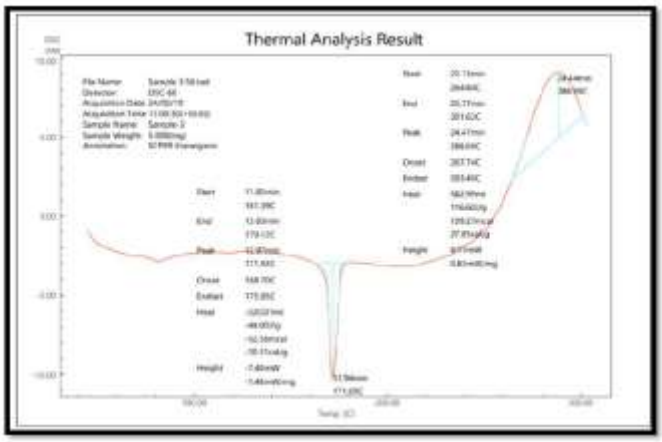


Fig. 7: DSC Thermogram of Paracetamol +Excipients.

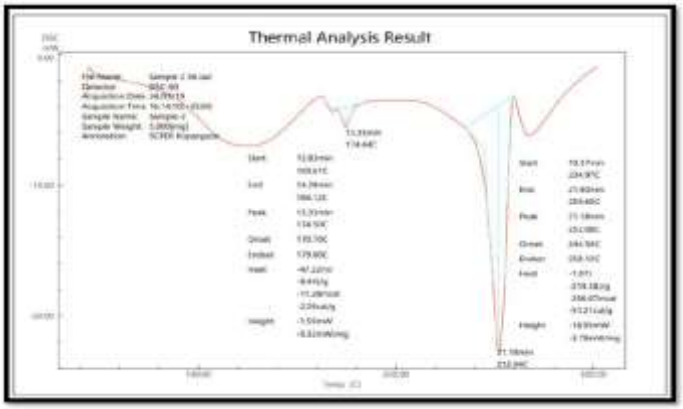


Fig. 8: DSC Thermogram of API Acyclovir.

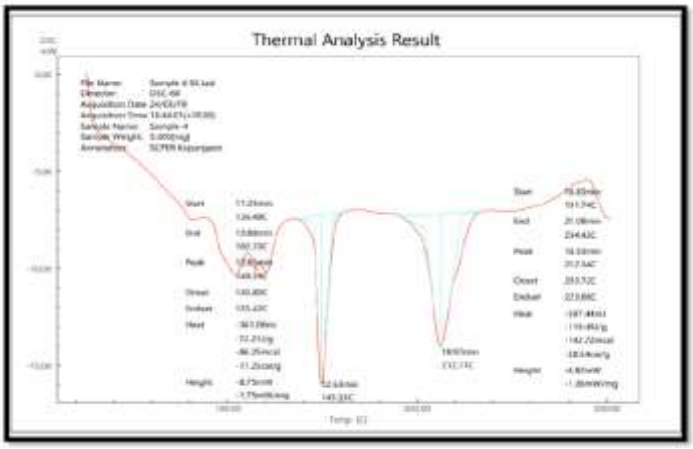


Fig. 9: DSC Thermogram of Acyclovir +Excipients.

FT-IR Study

FTIR spectrum reveals characteristic absorption peaks of Paracetamol and Acyclovir at different wave numbers in different samples.

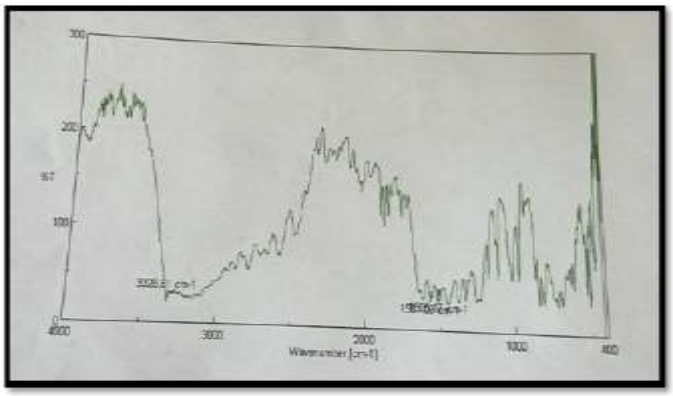


Figure 10: FT-IR spectra of API Paracetamol.

Table 5: Interpretation of infrared spectra of paracetamol.

Sr. No	Wave Number (cm^{-1})	Interpretation
1.	3326.61	O-H stretching
2.	3165.21	C-H stretching
3.	1502.32	N-H stretching

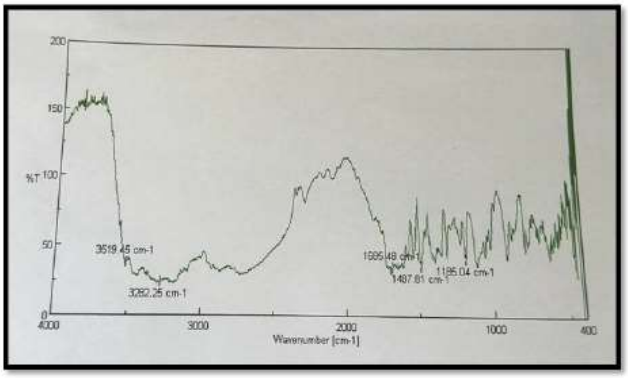


Figure 11: FT-IR spectra of API Acyclovir.

Table 6: Interpretation of infrared spectra of acyclovir.

Sr. No.	Wave Number (cm^{-1})	Interpretation
1.	3619.45	OH stretching
2.	3282.25	CH- stretching
3.	1685.48	C=O group
4.	1487.81	NH2 group
5.	1195.04	C-N stretching

Pre-compression parameters for granules

Precompression parameters of Immediate release layer and Sustained release layer granules shows Angle of repose, Carr's index, Hausner's ratio are in the range given in official standards.

Table 7: Pre compression parameters for sustained release layer granules.

Formulation	Bulk density(g/ml)	Tapped density(g/ml)	Carrs index (%)	Hausnersratio	Angle of repose (θ)
SR1	0.43±0.002	0.47±0.004	8.5±0.11	1.09±0.032	23.26±0.23
SR2	0.43±0.005	0.47±0.006	8.5±0.11	1.09±0.033	23.74±0.23
SR3	0.42±0.004	0.47±0.005	10.63±0.13	1.11±0.034	23.17±0.23
SR4	0.44±0.003	0.49±0.007	10.20±0.14	1.11±0.032	23.26±0.24
SR5	0.43±0.010	0.46±0.004	6.52±0.11	1.06±0.032	22.78±0.22
SR6	0.43±0.004	0.47±0.004	8.51±0.11	1.09±0.032	22.29±0.23
SR7	0.44±0.008	0.47±0.004	9.7±0.03	1.10±0.033	22.26±0.23
SR8	0.43±0.004	0.47±0.004	4.2±0.02	1.10±0.032	23.74±0.24
SR9	0.44±0.005	0.48±0.005	8.3±0.05	1.09±0.032	24.22±0.23

Table 8: Pre-compression parameters for immediate release layer granules.

Formulation	Bulk density (g/ml)	Tappeddensity (g/ml)	Carrs index(%)	Hausnersratio	Angle ofrepose (θ)
IR1	0.74±0.005	0.79±0.008	13.63±0.41	1.06±0.025	26.31±0.26
IR2	0.78±0.006	0.82±0.008	4.87±0.08	1.07±0.045	28.64±0.19
IR3	0.77±0.005	0.81±0.006	5.89.±0.10	1.08±0.029	29.68±0.24
IR4	0.75±0.004	0.77±0.005	3.78±0.04	1.02±0.071	29.24±0.35

IR5	0.79±0.008	0.84±0.008	6.56±0.12	1.06±0.034	29.68±0.32
IR6	0.75±0.008	0.80±0.007	6.63±0.12	1.06±0.026	29.68±0.17
IR7	0.78±0.005	0.82±0.007	5.54±0.09	1.05±0.024	27.81±0.24
IR8	0.81±0.006	0.85±0.008	5.62±0.09	1.04±0.029	28.81±0.19
IR9	0.80±0.007	0.85±0.008	6.10±0.11	1.06±0.022	29.68±0.15

Post compression parameters for tablet-in-tablet

Table shows postcompressional parameters i.e. Weight variation, Thickness, Hardness, Friability, Drug content, Disintegration time within the acceptable official limits.

Table 9: Post compression pParameters of Tablet-in- tablet.

Batch	Uniformity ofweight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F1	698.95±1.5	4.81±0.04	5.1±0.05	0.22±0.04
F2	701.45±1.6	4.30±0.07	5.5±0.03	0.24±0.06
F3	699.35±1.5	4.28±0.14	5.3±0.07	0.28±0.02
F4	700.40±1.3	4.32±0.09	4.7±0.04	0.26±0.03
F5	650.56±1.3	4.31±0.02	5.9±0.05	0.24±0.02
F6	700.15±1.4	4.34±0.07	5.2±0.03	0.22±0.06
F7	698.90±1.5	4.28±0.03	4.5±0.02	0.26±0.04
F8	696.85±1.6	4.33±0.08	5.8±0.03	0.24±0.03
F9	700.05±1.6	4.30±0.06	4.1±0.03	0.28±0.06

***In-vitro* drug release study**

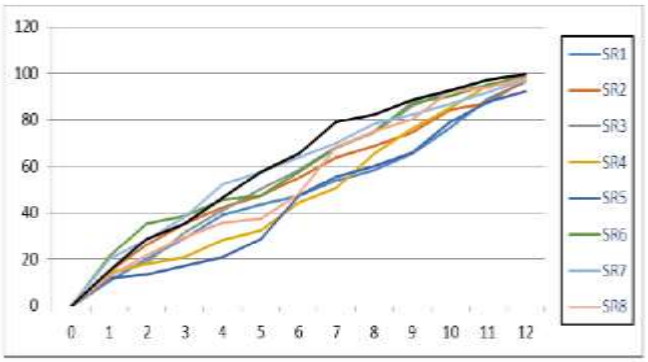
Table 10: *In-vitro* drug release studies formulations (SR1-SR9) (SRL).

Batch	Drug Content (%)		In vitro disintegration time (Sec)(IRL)
	SR	IR	
F1	89.60±0.29	89.66±0.68	30±1.00
F2	90.22±0.54	90.45±0.46	27±1.70
F3	91.17±0.49	91.56±0.49	29±1.01
F4	93.65±0.47	93.45±0.35	48±1.55
F5	92.92±0.25	92.23±0.56	49±1.09
F6	95.63±0.15	92.73±0.35	34±1.01
F7	96.31±0.44	90.90±0.81	29±1.00
F8	97.49±0.17	95.50±0.35	28±1.01
F9	99.90±0.58	98.02±0.56	30±1.00

Table 21:* In-vitro *Drug Release studies formulations (SR1-SR9) (SRL).

Time (hr)	Percentage Cumulative Drug Release profile (%)								
	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8	SR9
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	10.72	14.6	13.8	14.4	11.931	22.960	20.774	12.009	15.3
2	20.23	26.37	18.54	18.2	14.337	32.125	28.510	26.855	28.35
3	29.84	35.56	31.27	21.51	17.040	36.451	39.556	35.779	35.41
4	38.95	42.36	41.47	28.15	21.043	43.500	51.643	41.143	46.35

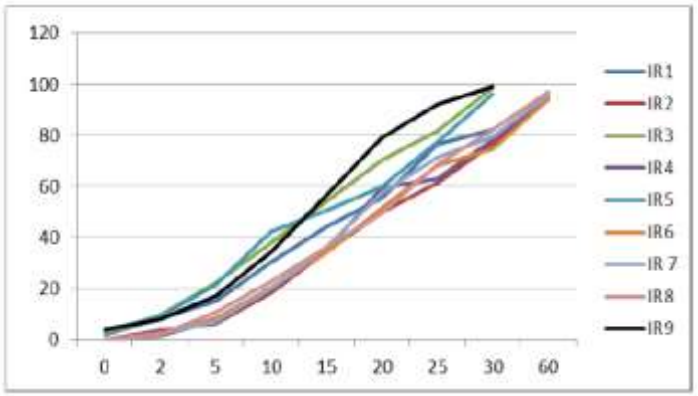
5	43.6	47.24	50.41	32.56	26.069	47.778	56.772	55.746	57.48
6	47.1	55.29	58.84	44.58	29.260	58.928	62.145	67.964	65.54
7	54.74	63.86	68.47	50.74	42.650	66.110	70.585	72.081	79.28
8	58.65	68.74	74.54	68.14	50.342	72.904	77.012	78.663	82.31
9	65.63	74.35	86.57	76.58	65.523	78.711	81.022	82.159	88.21
10	76.21	84.57	92.78	85.47	76.181	87.978	86.577	88.141	92.5
11	88.9	87.35	94.2	94.71	86.995	93.581	91.681	94.535	97.54
12	96.3	97.25	99.7	96.37	94.327	98.407	98.422	98.071	99.8



Percent Cumulative Drug Release from batch (SR1-SR9).

Table 10: *In-Vitro* Drug Release studies formulations (IR1-IR9) (IRL).

Time	Percentage Cumulative Drug Release profile								
	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8	IR9
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	2.016	3.47	2.48	1.37	3.21	2.51	2.3	1.85	3.92
5	8.86	6.44	9.65	7.45	9.23	18.38	7.25	10.9	12.47
10	15.08	18.4	22.3	18.74	21.41	20.41	19.74	22.8	34.5
15	29.33	34.64	38.1	34.69	42.35	34.16	36.34	36.5	49.23
20	44.09	49.85	54.35	51.82	50.81	57.90	57.77	49.6	66.23
25	55.54	61.31	70.15	63.11	59.21	69.29	71.23	68.5	79.27
30	68.24	76.25	81.84	78.54	77.45	87.15	79.27	82.27	88.85
60	82.35	89.27	92.74	95.62	87.48	94.54	95.84	97.21	98.24



Time (min)

Percent cumulative drug release from batch (IR1-IR9).

Release kinetics

Release kinetics for sustained release layer

Dissolution data of the optimized batch SR9 was fitted to varoius mathematical models like zero-order, First-order, Higuchi, Korsmeyer-Peppas and Hixson Crowell model in order to describe the kinetics of drug release. Smallest value of sum of squared residuals (SSR), PCP dissolution software and best goodness-of-fit test (R^2) were taken as crtieria for selecting the most appropriate mode. Zero order kinetic model were the best fit model for batch SR9.

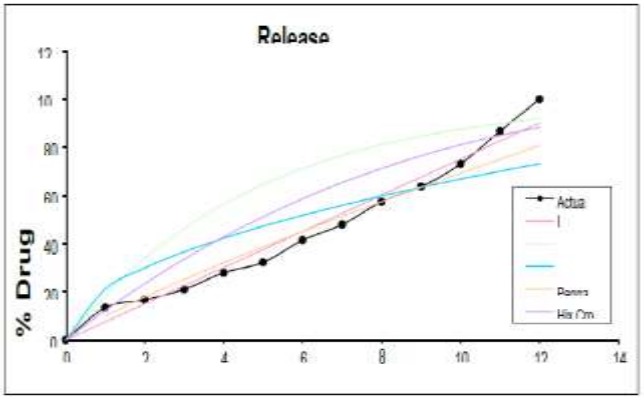


Fig. 12: In vitro Drug Release of SR9 optimize formulation.

Table 11: Kinetics Release of SR9 optimize formulation.

Models	Zero order	1st order	Matrix	Korsmeyer-Peppas	Hixon-Crowel
R^2 value	0.9884 (Best fit model)	0.6794	0.8979	0.9721	0.8497

Release kinetics for immediate release layer

Dissolution data of the optimized batch IR9was fitted to varoius mathematical models like zero-order, First-order, Higuchi, Korsmeyer-Peppas and Hixson Crowell model in order to describe the kinetics of drug release. Smallest value of sum of squared residuals (SSR), PCP dissolution software and best goodness-of-fit test (R^2) were taken as crtieria for selecting the most appropriate mode. Matrix order kinetic model were the best fit model for batch IR9.

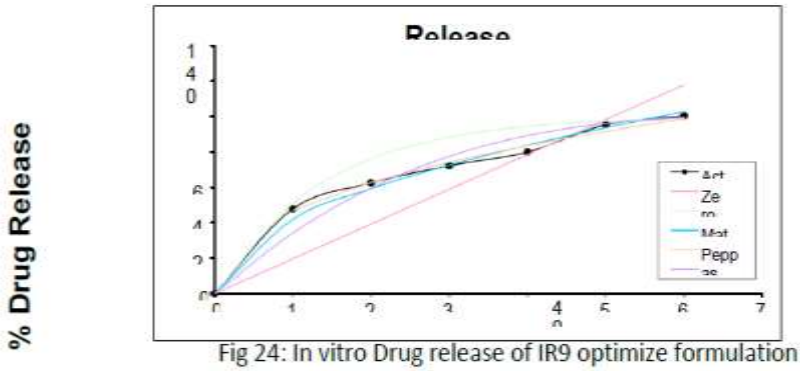


Fig 24: In vitro Drug release of IR9 optimize formulation

Table 13: Kinetics Release of IR9 optimize formulation

Models	Zero order	1st order	Matrix	Korsmeyer-Peppas	Hixon-Crowel
R^2 value	0.8587	0.8690	0.9951 (Best fit model)	0.9934	0.9734

SUMMARY AND CONCLUSION

The present study was aimed to develop Tablet-in-tablet tablet of Paracetamoland Acyclovir. Tablrt-in-Tabelt tablet were formulated to reduce frequency of administration.The tablets were formulated using superdisintegrant such as Sodium Starch Glycolate in immediate release and polymers such as HPMC k4M and HPMC K15M in sustained release.Tablet-inTablet tablets were prepared by wet granulation.

- The drug-excipient compatability studies confirmed that both drugs are compatible with excipients by DSC. Preformulation study was carried out for selected drugs.
- The formulated granules were evaluated for precompression studies which showed that the flow property was good.
- The formulated Tablet-in- tablet can be used for used for treatment of chickenpox.
- All the formulations were evaluated for physical characteristics, drug content, dissolution, release kinetics and stability study.
- The tablets were formulated by wet granulation technique.
- The formulated tablets were found within the limits with respect to uniformity of weight, hardness, thickness and friability.
- The drug content of the Tablet in Tablet were estimated by simultaneous estimation and it was within limits.
- Based on in vitro dissolution studies, Immediate Release formulation IR9 was optimized and selected which contains Sodium Starch Glycolate(25%) as super disintegrant, drug release was found to be 99.83% drug release within 60min. a

- To reduce the frequency of administration and to improve patient compliance, a Tablet-in-tablet tablet was prepared sucessfully.
- So, from immediate release study formulation IR9 and from sustained release study formulation SR9 were selected as best formulation of each layer.

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