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Formulation and evaluation of acyclovir sustained release matrix tablets

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ABSTRACT

The aim of the present work is to Formulate and Evaluate controlled release of Acyclovir matrix tablets used for treatment of viral infections. Development of SR Acyclovir is proposed considering the adverse event profile and high fluctuation index of Acyclovir observed with SR dosage forms. In the present work, attempts were made to formulate and evaluate controlled release of matrix tablets of Acyclovir. Acyclovir was subjected to preformulation studies, based on the results obtained Acyclovir controlled release tablets were successfully formulated. Formulations prepared by direct compression technique using sodium alginate and xanthan gum as control release polymers. Set of trials were formulated for which Acyclovir evaluated parameters (bulk density, tapped density, compressibility index, hausner's ratio, weight, thickness, hardness) were found to lie within the specifications Dissolution study was performed in USP type II apparatus at 100 RPM in 0.1 HCL for 2 hours followed by pH 1.2 and pH 6. 8 phosphate buffer. From the results of the invitro study it appears that the release of the Acyclovir was significantly influenced by the characteristics of the polymer used.

Keywords: Acyclovir, Polymers, Direct compression technique, in vitro drug release studies, Zero order kinetics.

INTRODUCTION[1, 2, 3, 4,]

Oral drug formulations, such as solid unit dosage form like tablets and capsules. They are prepared and release the active drug quickly after oral administration, to produce speed and total systemic drug absorption. After administration of drug it enter into the systemic circulation after that drug will be absorbed from the tablets or capsule dosage form is complete, concentrations of drug plasma reduce according to the drug's pharmacokinetic profile. Finally, drug plasma concentrations drop below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before it reaches to the point, further dose is usually given if a sustained therapeutic effect is disparate. An unconventional to operate further dose is to use a dosage form that will supply controlled drug release, and therefore maintain plasma drug concentrations. Various types of extended drug release products are identified:1. *Extended-release drug products*. The drug dosage form that is enters at least a binary depletion in dosage extensiveness as compared to that drug as an immediate-release (conventional) dosage form. 2. *Delayed-release drug products*. The drug release from dosage form in a portion of drug in to the systemic circulation after oral administration. Enteric-coated dosage forms are the most common delayed-release products. 3. *Targeted-release drug products.* The drug release from dosage form at or near conscious physiologic site of action. This dosage may have either immediate- or extended-release characteristics.

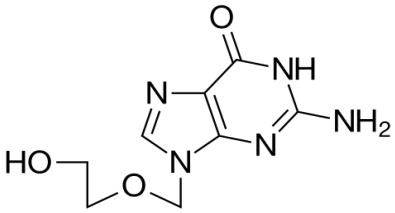
Sustained drug delivery system

Sustained drug contains loading dose and maintaince dose. In that loading dose is quickly released to form speed drug on site if action and maintaince dose is released at a sustained release rate so that the plasma concentration persist continual above minimum effective concentration [2, 3.Types] of oral sustained release drug delivery systems: Diffusion, Dissolution, Diffusion, and dissolution systems, Osmotically Gastro retentive drug delivery systems, electri cally stimulated release devices, Ion-exchange resins. Factors influencing the design and performance of Sustained release products**:** Physicochemical factors: Aqueous solubility, Partition coefficient, Drug stability, Protein binding,

Molecular size and Diffusivity. Biological factors: Absorption Distribution, Elimination Biological half life and Duration of action, Side effects and Margin of safety, Dose size, Disease state.Following studies carried out are: Preformulation studies, Preformulation study of Acyclovir, Organoleptic Properties, Melting point of drug, Determination of solubility. Evaluation of blends: Bulk density, Tapped density, Angle of repose, Carr's Index Compressibility Index), Hausner's Ratio. Preparation of sustained release tablets by using various concentrations of Polymers. Direct compression Technique. Evaluation of Matrix tablets: Thickness, Hardness, Weight variation, Friability, In-vitro drug release study, Stability studies.

DRUG PROFILE

Name: Acyclovir
Functional category: Anti viral agent
Structural formula: Molecular formula: $C_8H_{11}N_5O_3$
Structure: Acyclovir



Description: A guanosine analog antiviral drug that acts as an antimetabolite. Acyclovir is used for the treatment of herpes simplex virus infections, varicella zoster (chickenpox) and herpes zoster (shingles).
Solubility: Soluble in water and insoluble in organic solvents.
Mechanism of action: Viral (HSV-1, HSV-2 and VZV) thymidine kinase converts acyclovir to the acyclovir monophosphate, which is then converted to the diphosphate by cellular guanylate kinase, and finally to the triphosphate by phosphoglycerate kinase, phosphoenolpyruvate carboxykinase,and pyruvate kinase. Acyclovir triphosphate competitively inhibits viral DNA polymerase and competes with the natural deoxyguanosine triphosphate.
Uses: Acyclovir is used for the treatment of herpes simplex virus and varicella zoster virus infections, Herpes of the eye and herpes simplex blepharitis (a chronic (long-term) form of herpes eye infection)

MATERIALS AND EQUIPMENT

Aciclovir- Hetero labs, HYD, Sodium alginate- AR Chemicals, HYD, Xantham gum -AR Chemicals, HYD, Lactose-AR Chemicals, HYD, Micro crystalline cellulose - AR Chemicals, HYD, Talc-AR Chemicals, HYD, Magnesium Stearate-AR Chemicals, HYD.

EQUIPMENT

UV/VIS Double beam Spectrophotometer- Lab India – Double beam UV/VIS Spectrophotometer, Hyderabad, FTIR- Shi Pfizer shardness tester madzu, Tap Density Tester- Electro Lab, Tablet dissolution tester USP- Lab India-DS 8000, Hydraulic Press- Kimaya Engineers, Weighing balance- Afcoset ER-120A, Hardness tester-Pfizer shardness tester, Friability tester- Roche friability tester.

METHODOLOGY

Preformulation study: Preformulation studies were performed on the drug, which include melting point determination, solubility and compatibility studies. Determination of melting point.

Table 1: Preparation of sustained release Acyclovir tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8
Drug	200	200	200	200	200	200	200	200
Tragacanth	100	-	-	50		-	50	50
Sodium alginate	-	100		-	50	50	-	50
Xanthan gum	-	-	100	-	-	50	50	-
Microcrystalline cellulose	195	195	195	245	245	195	195	195
Talc	2	2	2	2	2	2	2	2
Magnesium Stearate	3	3	3	3	3	3	3	3
Total wt	500	500	500	500	500	500	500	500

Preparation of matrix tablets by Direct compression method: Different matrix embedded formulations of Acyclovir were prepared by direct compression method using varying proportion of polymers. The ingredients were passed through a 60 mesh sieve. Calculated amount of the drug, polymer and filler (MCC) was mixed thoroughly. Magnesium stearate was added as lubricant, the appropriate amount of the mixture was weighed and then compressed using a an Ten station rotary press at a constant compression force equipped with a 10-mm flat-faced punches at a compression force required to produce tablets of about 5–8 kg/cm^2 hardness. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

Evaluation studies

Pre compression parameters: Determination of bulk density and tapped density, Angle of repose, Thickness, Hardness, Friability: Content Uniformity:

In- Vitro Release study

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 1.2 for the first 2 hrs, followed by pH 6.8 for remaining period of time. Temperature maintained at 37±5.The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask and make the volume with distilled water. The diluted samples were assayed at 225 nm against reagent blank.

Drug release kinetics

Several theories and kinetic models describe the dissolution of drug from immediate release and modified release dosage forms. There are several models to represent the drug dissolution profiles where f (t) is a function of time related to the amount of drug dissolved from the pharmaceutical dosage form. The quantitative interpretation of the values obtained in the dissolution assay is facilitated by the usage of a generic equation that mathematically translates the dissolution curve function of some parameters related with the pharmaceutical dosage forms. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time‘t’ or Q(t). Some analytical definitions of the Q(t) function are commonly used, such as zero order, first order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell models. These models are used to characterize drug dissolution/release profiles.

RESULTS AND DISCUSSION

Sustained release matrix tablets of Acyclovir were prepared and evaluated. In the present study 8 formulations with variable concentration of polymer were prepared and evaluated for physic-chemical parameters, In-vitro release studies and stability studies. Preformulation studies: Organoleptic evaluation Description: powder, Tast:Tastless, Odour: Odourless, Color: white, Determination of melting point: Melting point of Acyclovir was found in the range of 255 ^{0}c, which complied with the standard, indicating purity of the drug sample.c) Solubility: Soluble in diluted hydrochloric acid, slightly soluble in water; insoluble in alcohol. **Preparation of standard curve of Acyclovir** Standard curve of Acyclovir was determined by plotting absorbance V/s concentration at 225 nm. Using solution prepared in pH 6.8 at 225 nm. And it follows the Beer’s law.

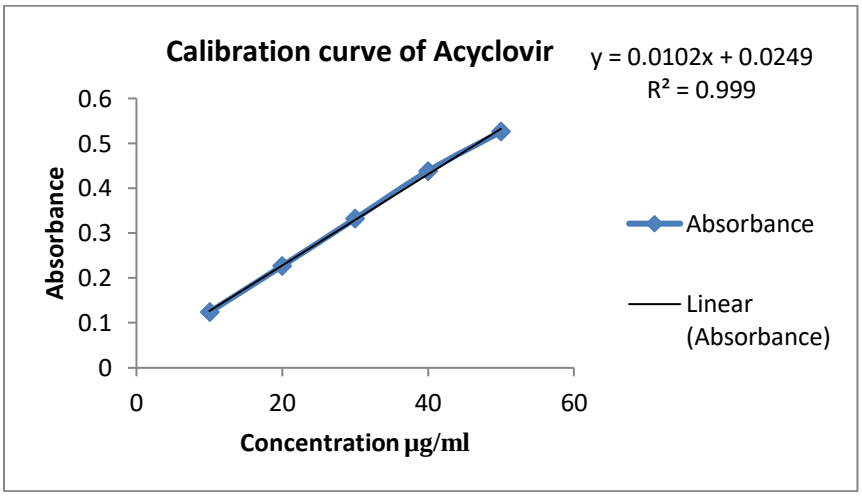


Fig 1: Calibration curve of Acyclovir

Evaluation studies: Pre compression parameters: Bulk Density: The found in the range of 0.418-0.428. Tapped density: The tapped density found in the range of 0.524-0.539. Angle of repose: It concludes that the entire formulations blend was found to be in the range of 27 ^{0} to3^{0}Compressibility index: found between 10% to 20.59 % indicating the powder blend have the required flow property for compression**.**

Table 2: Results for pre-compression parameters:

S.No	Bulk density	Tapped density	Compressibility index	Hausner’s ratio	ANGLE OF REPOSE(0)
F1	0.426	0.531	19.77	1.24	30^0
F2	0.419	0.521	19.57	1.24	28^0
F3	0.424	0.530	20.00	1.25	27^0
F4	0.422	0.528	20.07	1.25	29^0
F5	0.418	0.524	20.22	1.25	30^0
F6	0.429	0.540	20.55	1.25	31^0
F7	0.428	0.539	20.59	1.25	27^0
F8	0.423	0.529	20.03	1.26	30^0

Post compression parameters

Weight variation: All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.Thickness:Tablets mean thickness were uniform in F1 to F8 formulations and were found to be in the range of 4.56 mm to 4.88 mm. Hardness: The measured hardness of tablets of each batch ranged between 5.17 to 5.28 kg/cm^2.This ensures good handling characteristics of all batches. Friability: The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable. Content Uniformity: The percentage of drug content for F1 to F8 was found to be between 89.55% and 98.92 % of Acyclovir, it complies with official specifications.

Table 3: Physical parameters of tablets of each batch

F. No.	Weight variation (mg)*	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Drug content (%)
F1	500	4.86	5.28	0.45	91.85
F2	499	4.78	5.19	0.51	97.20
F3	498	4.59	5.25	0.48	96.22
F4	500	4.78	5.21	0.46	91.88
F5	499	4.56	5.19	0.43	93.89
F6	500	4.86	5.17	0.50	89.55
F7	499	4.75	5.20	0.51	92.55
F8	500	4.88	5.22	0.49	98.92

In-vitro Dissolution Study

All the eight formulation of prepared matrix tablets of Acyclovir were subjected to in-vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for the 8 hrs.

Table 4: Dissolution Profile of F1 to F8

Time (hrs.)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
0	0	0	0	0	0	0	0	0
1	29.12	28.20	27.11	28.09	27.89	26.94	25.19	29.18
2	32.45	35.30	33.11	31.45	32.28	36.15	35.14	36.95
3	42.80	45.32	43.76	49.90	41.28	43.69	42.16	48.16
4	52.63	54.65	53.23	59.70	50.71	52.18	50.31	57.16
5	68.21	69.28	62.11	65.16	61.46	62.17	63.18	62.18
6	73.35	78.55	75.22	71.22	70.25	71.28	70.19	78.16
7	88.26	83.10	85.16	80.26	82.19	83.14	82.15	82.28
8	92.25	92.99	95.12	93.50	92.17	93.18	91.18	95.12

Table 5: Mechanism of drug release

S.NO	time	log T	Square root of Time	%CR	%Drug remaining	log %CR	LOG% drug retained	cube root of %drug remaining
0	0	0	0	0	100	0	2	4.641589
1	1	0	1	29.18	81.57	1.265525	1.91153	4.336874
2	2	0.30103	1.414214	36.95	59.46	1.607884	1.774225	3.903088
3	3	0.60206	2	48.16	35.35	1.810569	1.548389	3.281934
4	4	0.778151	2.44949	57.16	21.63	1.89415	1.335057	2.786242
5	5	1	3.162278	62.18	10.53	1.951677	1.022428	2.191843
6	6	1.125681	3.464102	78.16	3.72	1.983536	0.570543	1.549462
7	7	0.26456	2.36987	82.28	56.39	1.89415	1.025060	2.25986
8	8	0.778151	1	95.12	15.28	1.93285	1.022428	2.191843

Stability studies

Sustained release matrix tablets of Acyclovir formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient humidity conditions, at room temperature, at 40^{o}c and 2-8^{o}c for a period up to 90 days.

Table 6: Results of stability studies of optimized formulation F-8

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-8	25^{0}C/60%RH % Release	95.12	95.11	95.10	95.08	Not less than 85 %
F-8	30^{0}C/75% RH % Release	95.12	95.10	95.09	95.06	Not less than 85 %

F-8	40^0C/75% RH % Release	95.12	95.10	95.08	95.06	Not less than 85 %

CONCLUSION

The present study was undertaken with an aim to formulate and evaluate Acyclovir sustained release tablets using different polymers as release retarding agents. Preformulation study was carried out and all the parameters were found within the specification. Hence different batches of Acyclovir were prepared using selected excipients. Powders were evaluated for Bulk density, tapped density, compressibility index, Hausner's ratio before being punched as tablets. Various formulations of sustained release tablets of Acyclovir were prepared by using different polymers viz tragacanth, sodium alginate and Xanthan gum in different proportions by Direct compression technique. The tablets were evaluated for physical parameters, *in vitro* release study and stability studies. In-vitro release indicated that the formulation F8 had better dissolution profile along with sustained action as compare to other formulations. Stability study was conducted on tablets of Batch F8 stored at room temperature, 40^0C, and 2-8^0C for one month. Tablets were evaluated for hardness, friability, in-vitro release profile and drug content. No significant changes were observed in any of the studied parameters during the study period (90days), thus it could be concluded that formulation was stable.

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