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FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF ANTIVIRAL DRUG-ACYCLOVIR

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ABSTRACT

The floating tablet containing Acyclovir were successfully prepared by using different polymers Guar gum and Ethyl cellulose by direct compression method. MCC was used as diluents. The physiochemical evaluation results for the granules of all trials pass the official limits in angle of repose, compressibility index indicating passable flow property. The prepared dry mixer for floating tablets were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation F7 contains the average thickness of 3.05mm, average hardnes 7.1kg/cm^2, friability of 0.12%. Although the Buoyancy lag time of formulation was 5 minutes, it released the acyclovir in sustained manner up to 12 hours. The *in Vitro* dissolution profiles were found to extend the drug release over a period of 12 hours and the drug release was found to decrease with an increase in concentration of polymer.

Key words: oral thin film, Sumatriptan succinate, folding endurance

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INTRODUCTION

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either local or systemic action. All the pharmaceutical products formulated for systemic Delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug (ii) the anatomic and physiologic characteristics of the gastrointestinal tract and (iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed.

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and

predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDFs or GRDS). GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form. Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring about new and important therapeutic options such as – This application is especially effective in sparingly soluble and insoluble drugs, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes affecting drug absorption. To override this problem, erodible, gastro retentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site. GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the sub mucosal tissue of stomach) GRDFs can be used as carriers for drugs with so-called absorption windows. These substances for e.g. antiviral, antifungal and antibiotic agents are taken up only from very specific sites of the GI mucosa. Floating Drug Delivery System (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems (1-6).

The present investigation applied a systematic approach to the development of floating drug delivery system of Acyclovir as an antiviral agent.

MATERIALS AND METHODS

Drug Excipient Compatibility Study (7-10)

A Successful formulation of a stable and effective solid dosage form depends on careful selection of the excipients that are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies are of paramount importance. Drug excipient compatibility studies were carried out by mixing the drug with various excipients in different proportions was placed in a vial; rubber stopper was placed on the vial and sealed properly. Studies were carried out in glass vials at accelerated conditions, 40^0 C± 2^0 C/75 ±5%RH and a storage period of 4 weeks. After storage, the samples were observed physically for discoloration and degradation.

Formulation of floating Tablets

The tablets containing 100mg Acyclovir were prepared with a total tablet weight of 400mg.

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Procedure

Micro crystalline cellulose and different polymers were weighed and sifted through 40 mesh according to the formulation table-1. To the above blend Acyclovir was added and sifted through 18 mesh. The sifted materials were mixed for 10min. Magnesium Stearate and talc was weighed and sifted separately through 40 mesh. To the above mixture, lubricated blend was added and mixed properly. Then the blend was compressed using 16*8mm oval punch.

Table-1 Formulae for Acyclovir Floating tablets (F1 to F9)

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Acyclovir	100	100	100	100	100	100	100	100	100
HPMC(K4M) (%)	20	--	--	--	20	--	--	25	25
Guar gum (%)	--	20	--	20	--	25	25	--	--
Carbopol (%)	--	--	20	--	--	--	--	--	
EC (%)	--	--	--	5	5	5	10	5	10
PVP K30 (%)	5	5	5	5	5	5	5	5	5
Sodium bicarbonate (%)	15	15	15	15	15	15	15	15	15
MCC	qs	qs	qs	qs	qs	qs	qs	qs	qs
Talc (%)	2	2	2	2	2	2	2	2	2
Magnesium stearate (%)	2	2	2	2	2	2	2	2	2
Total weight	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg

In vitro Buoyancy studies

The in vitro buoyancy was determined by floating lag time, and total floating time. The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time the tablet constantly floats on the dissolution medium was noted as the Total Floating Time respectively (TFT).

***In vitro* Dissolution Studies for floating tablet of Acyclovir**

In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 8hr, at 50 rpm, 0.1 N HCl (pH 1.2) was used as a

dissolution medium. 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 254nm.

RESULTS AND DISCUSSION

From the drug excipient compatibility studies it was observed that there was no change in physical appearance of the drug. This indicates that the drug was compatible with all the formulation components (Table-2).

Table-2 Results of Drug - Excipient Compatibility Studies

S.NO.	COMPOSITION DETAILS		OBSERVATION			
			STORAGECONDITION/DURATION			
		INITIAL	40^0C/75%RH			60^0C
			1M	2M	3M	4M
1	ACYCLOVIR	White crystalline powder	NCC	NCC	NCC	NCC
2	ACYCLOVIR+HPMC	White crystalline powder	NCC	NCC	NCC	NCC
3	ACYCLOVIR+ MCC	White crystalline powder	NCC	NCC	NCC	NCC
4	ACYCLOVIR+SODIUM BI CARBONATE	White crystalline powder	NCC	NCC	NCC	NCC
5	ACYCLOVIR+ ALL EXCIPIENTS 1:1	White crystalline powder	NCC	NCC	NCC	NCC

The powder blend of all the formulations was evaluated for angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The angle of repose was found to be in the range of 25.14± 1.17 to 27.82±1.14. It indicates that powder blend have a good flow property. The bulk density and tapped density were found to be 11.63±1.14 to 14.94±0.15 and 1.13± 0.05 to 1.18±0.02. All the results (Table-3) of pre compression parameters were within the prescribed limit indicating good flow properties of the powder blend. From the above pre-compression parameters it was clear evidence that drug and excipients has good flow properties so direct compression method was preferable.

Table-3 Data for Pre Compression Parameters of Acyclovir

Formulation code	Angle of Repose (θ)	Loose Bulk Density (g/cc)	Tapped Density (g/cc)	% Compressibility	Hausner's ratio
F1	24.6	0.45	0.52	13.4	1.15

F2	26.9	0.44	0.52	15.3	1.18
F3	24.2	0.45	0.51	11.7	1.13
F4	29.5	0.44	0.50	12.0	1.13
F5	20.6	0.45	0.52	13.6	1.15
F6	22.6	0.43	0.50	14.0	1.16
F7	23.1	0.44	0.52	15.3	1.18
F8	22.14	0.45	0.50	12.23	1.11
F9	23.01	0.44	0.50	12.58	1.13

Prepared tablets were evaluated for Hardness, Thickness, Friability and Buoyancy lag time, Total floating time, swelling index and in-vitro dissolution studies (Table-4). The Hardness of the tablets ranges from 6.4 to 7.2kg/cm^2. Thickness of all formulations lies between 2.80 to 3.05mm. The friability of all formulations ranges from 0.01% to 0.27%. Buoyancy lag time starts from 5 minutes to 13 minutes for all tablets and the total floating time for all formulations starts from 8 hours to more than 12 hours.

Table-4 Data for Post compression parameters of Floating tablets

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Buoyancy Lag time (min)	Total floating time(hrs)
F1	6.8	2.96	0.12	12	08
F2	6.4	2.80	0.15	09	08
F3	6.4	2.81	0.22	13	04
F4	7.1	3.01	0.17	10	10
F5	6.5	2.89	0.27	11	11
F6	7.2	3.01	0.25	08	>12
F7	7.1	3.05	0.12	05	>12
F8	7.0	3.05	0.14	09	>12
F9	6.9	2.85	0.01	08	>12

The prepared tablets were subjected to dissolution studies in order to know the amount of drug released and the data was presented in the Table-5. and the dissolution profiles of the formulations were shown in the figure 14. As the concentration of polymer increased, the drug release decreased. *In Vitro* drug release studies revealed that release of Acyclovir from different formulations varies characteristics and composition of polymers. The release rate decreased with increasing concentration of Guar gum and Ethyl cellulose in F4 to F7respectively. Formulations F4, F6 and F7 showed relatively high rate of release of drug which is due to rapid swelling of Ethyl cellulose.

Table-5 cumulative percentage drug release of F1 to F9

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	11.6	11.6	10.6	30.6	29.7	6.3	5.7	5.0	7.2
2	40.7	40.7	39.8	49.9	48.2	15.4	11.9	30.6	17.1
3	68.2	68.2	70.3	60.2	59.3	26.1	20.2	41.4	29.2
4	86.6	76.1	100.1	69.1	70.8	40.6	30.5	69.7	50.8
5	99.5	84.5	_	78.2	89.6	61.1	48.9	90.2	73.7
6	_	99.1	_	90.1	100.3	73.1	52.2	100.3	81.22
7	_	_	_	100.1	_	89.92	62.1	_	90.26
8	_	_	_	_	_	99.5	70.8	_	99.9
10	_	_	_	_	_	_	88.1	_	_
11	_	_	_	_	_	_	100.1	-	_

CONCLUSION

GRFDDS offer a simple and practical approach to achieve increased gastric residence and to modify drug release profiles essential for sustained, site specific and localized drug action. Floating tablets, in general have the potential to be used for controlled release drug delivery, but coupling of floating properties to tablet has additional advantages, e.g. efficient absorption and enhanced bioavailability of the drugs due to high surface to volume ratio, a much more intimate contact with gastric fluid. The floating tablet containing Acyclovir were successfully prepared by using different polymers Guar gum and Ethyl cellulose by direct compression method. MCC was used as diluents. The physiochemical evaluation results for the granules of all trials pass the official limits in angle of repose, compressibility index indicating passable flow property. The prepared dry mixer for floating tablets were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation F7 contains the average thickness of

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