Preparation and Evaluation of anti-viral drug Zanamivir using different polymers

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ABSTRACT

The dosage forms that stay in the stomach for longer period of time are much more effective to treat any disease. Thus, most approachable and feasible way is to prolong the drug delivery and controlling gastric residence time (GRT) and such kind of dosage forms are known as gastro retentive dosage forms (GRDF). The present study is focused to develop GRDF of Zanamivir. About four formulations of Zanamivir tablets were prepared with different ratios of drug and polymers. The prepared tablets were further evaluated on the basis of pre-compression and post-compression parameters. The dissolution study of the formulations revealed that formulation F3 using polymer (guar gum) showed 93.4% of in vitro drug release for 8 hours and is the optimized formulation. It was thus concluded that guar gum complies all the properties of floating tablets.

Keywords: *Zanamivir, Dissolution, Gastro retentive drug delivery system, First pass elimination, Influenza, Prophylaxis*

INTRODUCTION

Oral drug delivery system is considered to be one of the prevalent and efficaciously system due to its flexibility in designing the dosage forms with maximum therapeutic effects. For this, greater consideration has been paid on controlled drug delivery system. The controlled drug delivery system is defined as the type of dosage form where one or more drugs are released continuously in fixed way for precise time period and is targeted systemically or locally on specific organ [1,2]. The major advantages of controlled release dosage forms are that it provides maintenance of optimal and effective level of drug for prolonged time period and needs less frequency of dose with minimum side-effects [3]. There are few challenges in developing oral controlled drug delivery system such as developing drug delivery system, modulating gastrointestinal transit time and minimizing first pass elimination [4].

From last many years, the researchers and academicians are working on achieving prolonged and predictable drug delivery system in the gastrointestinal tract (GIT) and the feasible approach reported is to control gastric residence time (GRT) and formulate gastro retentive dosage forms (GRDF) [5,6]. The GRDF basically increases the release time period of drugs and also enhances the adherence level of patients. Some of the factors responsible for

controlling the gastric residence time are density and size of dosage form, shape of dosage form, single or multiple unit formulation, nature and frequency of meal, gender, age and posture [7]. The methods to increase the gastric retention time are named as- Floating system, Bio adhesive systems, swelling and expanding systems, High density systems, Modified systems. In this study, floating system has been used to prepare Zanamivir tablets and is defined as the system which have adequately resistance to float on gastric contents and persist resistant in the stomach and does not affect the rate of gastric emptying for longer period [8].

Zanamivir is the widely used anti-viral agent. It is the first neuraminidase inhibitor used for the treatment of influenza. Zanamivir (sialic analog) is found to be effective during clinical trials. It shortens the duration and decreases the severity of type A and type B influenza [9]. It is found as white crystalline powder which is highly soluble in water [10]. The half-life of Zanamivir is 2.5 hours to 5.1 hours [11]. It is usually used as the powder to inhale for the adults and children with age 7 years. Many studies proved that Zanamivir is effective against prophylaxis of influenza and it also provide symptomatic relief of influenza by reducing complications [12]. It has been reported that Zanamivir have uncertain benefits to reducing duration of illness with influenza [13].

MATERIALS AND METHODS

The chemicals used in this study were collected from laboratory of Sanskar College of Pharmacy, Ghaziabad (UP)

Standard graph of Zanamivir

Standard Stock solution: 100 mg of zanamivir was dissolved in 100 ml of 0.1N HCL (1000 µg/ml)

Calibration curve of Zanamivir in 0.1N HCl

1ml of stock solution was transferred into 10 ml volumetric flask and further the volume was adjusted upto 10 ml that matched to 100 µg/ml Zanamivir in solution. Then different aliquots of 2,4,6,8 and 10 ml were transferred to 10ml volumetric flask and volume was adjusted with 0.1N HCl that gave a concentration of 2,4,6,8, and 10 µg/ml of final standard. The standard curve was plotted after taking absorbance of secondary stock solutions in UV double beam spectrophotometer at 216 nm.

Formulation of Zanamivir tablets

The Zanamivir tablets were prepared by using direct compression method and various polymers. The composition of Zanamivir tablets has been shown in table 1. The 4 formulations were designed using different polymer ratios. The Zanamivir and other ingredients were mixed together and passed through sieve no.60 and then triturated for about 15 minutes. The powdered mixture was then mixed with magnesium stearate and tablets were prepared using direct compression method. The following table 1 shows ingredients and various formulations used for preparing Zanamivir tablets.

Table 1- Composition of formulations of Zanamivir tablets

Ingredients	**F1**	**F2**	**F3**	**F4**
Zanamivir	100	100	100	100
HPMC K4M	95	80	---	60
Guar gum	---	----	115	-----
Ethyl cellulose	---	----	----	80
PVP (Polyvinylpyrrolidone)	----	75	-----	-----
Sodium bi carbonate	30	30	30	30
Microcrystalline	120	60	100	75
Magnesium stearate	5	5	5	5
Total weight	350	350	350	350

Pre-compression evaluation parameters

Bulk density

It is defined as the weight of granules divided with the total volume of granules. It is measured by pouring the granules with the help of funnel and then measuring volume and weight of granules. It is expressed as g/cc. Mathematically, it is calculated as-

Bulk density= Weight of granules/ Bulk volume of granules

Tapped density

It is defined as weight of granules divided with the tapped volume of granules. It is measured by fixing the number of taps till the powder volume reach the minimum required volume. Mathematically, it is calculated as-

Tapped density = Weight of granules/ Tapped volume of granules

Hausner's ratio

It is used to analyze the flow properties of the powder and is defined as the ratio of tapped density to the bulk density of any powder. The following table 2 describes the flow properties of the powder or granules.

Mathematically, it is calculated as-

Hausner's Ratio = Tapped density / Bulk density

Table 2- Flow properties of powder or granules

Flow property	**Hausner's ratio**
Excellent	1.00-1.11
Good	1.1-1.18
Fair	1.19-1.25
Possible	1.26-1.34
Very poor	1.35 -1.45
Very very poor	>1.60

Post-compression evaluation parameters

The tables were evaluated on the basis of physicochemical properties and are defined as-

General appearance

The tablets were evaluated on the basis of color, odor, texture and shape.

Hardness

The hardness of the tablet was determined with the help of Monsanto hardness tester. The hardness tester was first set on zero reading and then lower plunger was placed on the table. The plunger was forced against the spring by turning the bolt till the tablet got fractured. The pointer with the guage rides indicating the force. Further, the reading was noted down.

Weight variation

Around 20 tablets were selected and weighed properly. The average weight was then calculated. The tablets were then compared with the average weight. Not more than weight of tablets should deviate from the average weight by more than 7.5% for 300 mg tablets and none of the tablet should have more than the double than that percentage.

Friability test

Around 20 weighed tablets were kept on the friability apparatus. After those 100 revolutions given to the tablets, the tablets were reweighed. Mathematically, percentage of friability was calculated by using following formula-

Percentage friability = initial weight-final weight /initial weight × 100.

Drug content

About 20 tablets were taken, weighed and powdered. 100mg of Zanamivir was then transferred to 100 ml of volumetric flask and volume was then adjusted to 100 ml with 0.1N HCl. After that, 1 ml of solution was diluted with 0.1 N HCl and the absorbance was observed at 216 nm.

In-vitro buoyancy studies

The floating lag time and total floating time was determined for in-vitro buoyancy. The tablets were placed in a beaker with 0.1N HCl. The time needed for the tablet to come to the surface and float was measured as floating lag time and the time taken by the tablet to float constantly was determined as total floating time.

Swelling index

The swelling index was measured by determining the weight gain in the dosage unit. The tablets were placed in each basket of dissolution apparatus in the dissolution medium 0.1N HCl at about 37±0.5° C. The tablet was then withdrawn from each basket after 1h, 4h and 6h. The excess water was removed with the help of blotted tissue paper and weighed using analytical balance. Mathematically, swelling index was calculated using following formula-

Swelling index= (Wet weight of tablet – Dry weight of tablet) / Dry weight of tablet

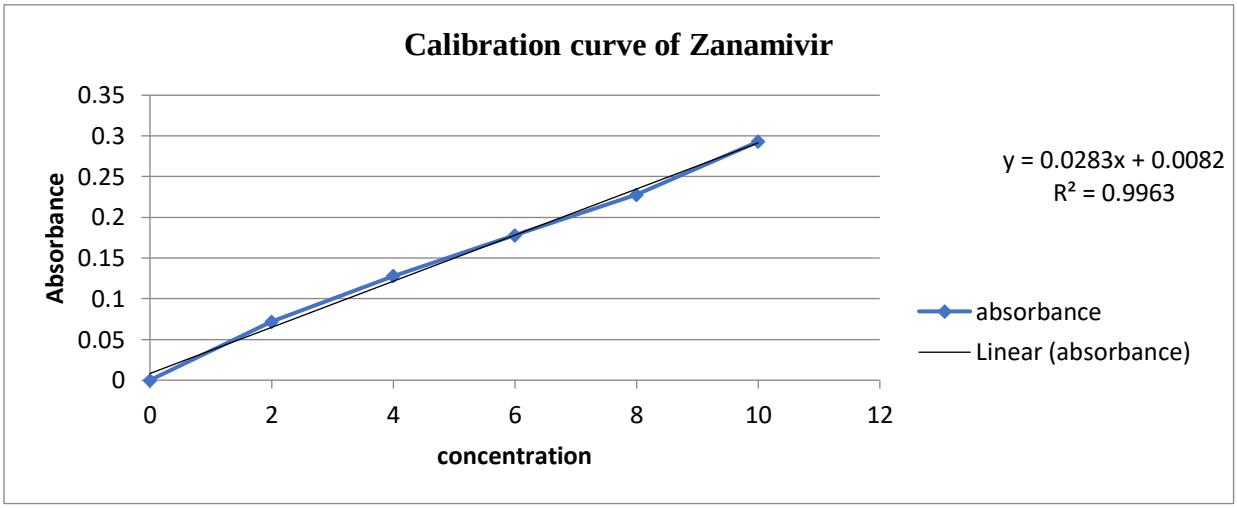
RESULTS AND DISCUSSION

Standard graph of Zanamivir

The following table 3 shows the absorbance level at different concentrations and the calibration graph has been shown in following graph 1

Table 3 Showing absorbance level at different concentrations

Concentration	Absorbance
0	0
2	0.072
4	0.128
6	0.178
8	0.228
10	0.293



Graph 1 Showing standard calibration curve of Zanamivir

Pre-formulation studies

The pre-formulation studies of powder such as bulk density, tapped density and hausner's ratio were done and the results are mentioned in table 4

Table 4 Showing pre-formulation studies of powder

Formulation	Bulk density	Tapped density	Hausner's ratio
F1	0.73	0.87	1.19
F2	0.75	0.87	1.16
F3	0.41	0.52	1.2
F4	0.45	0.50	1.1

Post-compression parameters

The post-compression parameters such as weight variation, hardness, friability test, drug content, buoyancy lag time and total floating time were done and the results are mentioned in table 5.

Table 5 Showing post-compression studies of Zanamivir tablets

Formulation	(Mean± S.D) (n=20)	Hardness (kg/cm2) (n=3)	Friability (n=6)	% Drug content (mg)	Buoyancy lag time (min)	Total floating time (hrs)
F1	351±0.4	7.2±0.4	0.546	98±0.7	25	7
F2	347±0.3	7.3±0.4	0.612	99±0.5	14	5
F3	346±0.8	7.6±0.6	0.525	99±0.6	60	7
F4	353±0.6	7.6±0.1	0.511	99±0.6	31	8

Swelling index

The selling index of Zanamivir tablets was calculated for different time intervals and is shown in table 6.

Table 6 Showing Swelling index of Zanamivir tablets

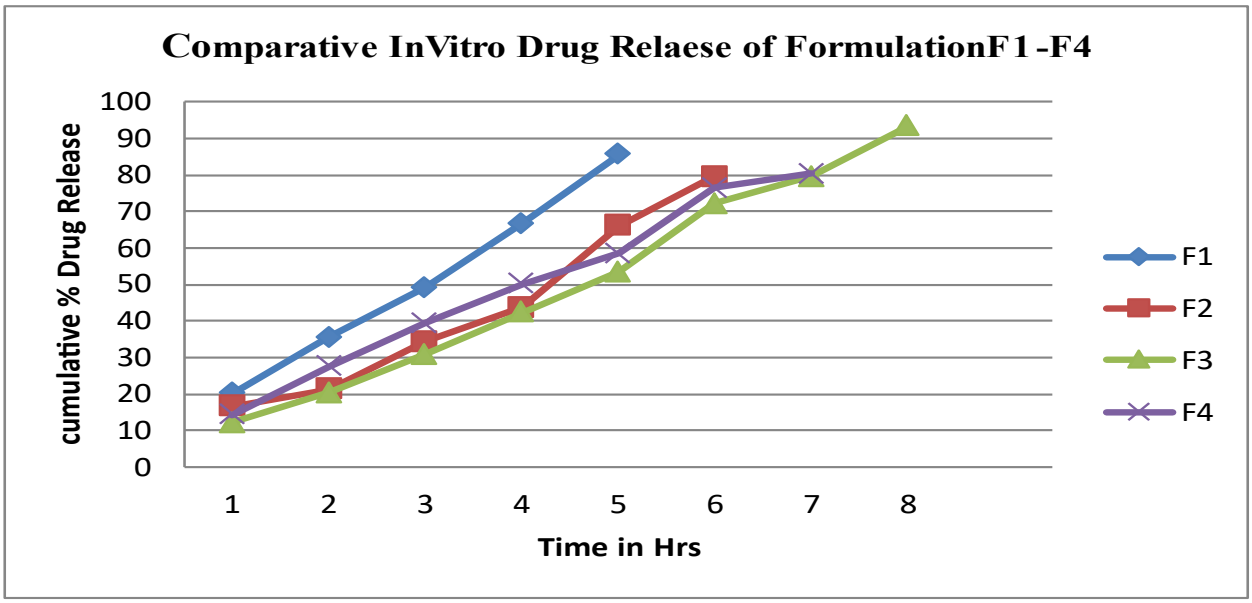
Time (hours)	F1	F2	F3	F4
0	0	0	0	0
2	33	32	43	56
4	45	48	51	60
6	55	54	61	65
8	48	50	55	59

Dissolution studies

The dissolution profile of Zanamivir tablets has been shown in table 7 and the % cumulative drug release profile of all the formulations have been shown in graph 2. The graph shows that formulation F3 has longer drug release for about 8 hours and is considered to be the optimized formulation as compared to other formulations F1, F2 and F4.

Table 7 Showing dissolution profile of Zanamivir tablets

Time (hours)	F1	F2	F3	F4
1	20.2	16.6	12.2	14.4
2	35.6	21.4	20.3	27.6
3	49.2	34.4	30.8	39.5
4	66.8	43.7	42.4	50.1
5	85.6	66.2	53.5	58.6
6	-	79.6	72.1	76.4
7	-	-	79.6	80.3
8	-	-	93.4	-



Graph 2 Showing comparative in-vitro drug release of Zanamivir tablets

CONCLUSION

The present study was aimed to prepare gastro retentive dosage form of Zanamivir tablets using different polymers. The effective of all the polymers were studied using various evaluations parameters. The dissolution study was also done on all formulations and it was found that F3 formulation was good and acceptable. The GRDF using guar gum as polymer could retain in the stomach for longer time period. The pre-compression and post-compression parameters of all four formulations exhibited satisfactory properties. Therefore- it can be concluded that floating tablets using guar gum is the optimized formulation and can be used to enhance the drug release in the stomach in controlled manner. The concept of floating tablets is one of the applied and appropriate approach to fulfill the objectives of gastro retentive floating tablets.

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CONFLICT OF INTEREST

The authors declare that there is no competing interest.

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