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Formulation of Tropisetron floating tablets for sustained drug release

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ABSTRACT

The objective of the present investigation was to formulate floating tablets of Tropisetron to delay and control the release of the drug in order to reduce the dosing frequency. The floating tablets were formulated using HPMC K15 and sodium CMC as the hydrophilic polymers and sodium bicarbonate as the gas generating agent. The thickness of all formulation was ranged in between 4.8 to 4.9 mm. Hardness of tablet of all formulation ranged from 5.2 kg/cm^2 and 5.6 kg/cm^2, friability in the range of 0.37% to 0.51%, weight variation in the range of 1.8 to 4.2 %. The *in vitro* buoyancy study suggests that all the formulations were able to float on the surface of the medium for more than 12 sec. The time required to reach the surface (lag time or float latency) was highest in HPMC containing formulations and was concentration dependent. Formulation F3 exhibited the highest lag time. The swelling of the formulations were affected by the polymer type with HPMC containing formulations exhibiting more swelling than the sodium CMC containing formulations. The formulations F1, F2 and F3 could maintain the drug release upto 9, 11 and 12 hours respectively whereas formulations F4-F7 could not sustain the drug release with all drug released by 7 hours.

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Introduction

The comparative ease of administration as well as the traditional belief is the reason for the popularity of oral route of drug delivery. The retention of orally administered dosage forms in the upper GIT leads to prolonging of the contact time of drug with the GI mucosa. This leads to attainment of higher bioavailability, and there by therapeutic efficacy, decreased time intervals for drug administration resulting in frequent dosing, significantly reduced dose size and hence superior patient compliance (Garg & Sharma, 2003).Therefore,extended release DDS which possess gastric retention properties are thought to be significantly useful (Rubinstein & Friend, 1994).

Tropisetron is a drug with high oral bioavailability but a rapid rate of metabolism and excretion. Around 80% of the drug is excreted in urine either unchanged or as metabolites and the half-life of the drug is 5.7 h (drugbank, 2021). The rapid excretion causes the requirement of higher doses of the drug. This makes it a potential candidate for improvement by appropriate formulation design. Floating tablets are known to reduce the dosing by sustaining the release of drug molecules as the formulation remains floating in the gastrointestinal tract and releasing the drug slowly. Several approaches have been studied for sustaining the release of drugs with a few able to achieve good results (Sharma et al., 2019; Thakur et al., 2019; Taneja and Gupta, 2017).

The objective of the work was to delay and control the release of the drug through the formulation and to reduce the dosage of the drug required.

Material and Methods

Preformulation Studies (Ahirwar et al., 2021)

Organoleptic properties

The organoleptic characters of the drug like color, odor, taste and appearance were observed using physical senses.

Solubility

Qualitative solubility was observed for Tropisetron in various solvents of changing polarity.

Melting point

The melting point of Tropisetron was determined using open capillary method.

Loss on drying (LOD)

Accurately weighed 1 g of Tropisetron was even spread in a watch glass and heated in a hot air oven at 100-105°C for 15 min. The drug was reweighed and the procedure was continued till two constant weights were obtained. Loss on drying was calculated using the formula:

$$\% LOD = \frac{Initial\ weight - Final\ weight}{Initial\ weight} X100$$

Compatibility Study

The physical and chemical compatibility among the drug and excipients was studied using FTIR spectra of the drug and the physical mixture of the drug and polymer.

Calibration Curve of Tropisetron (Jani et al., 2021)

10 mg Tropisetron HCl was weighed accurately and transferred to a 100ml volumetric flask. The final volume was made up to 100ml with distilled water to prepare the 100µg/ml stock solution.

From the above stock solution, aliquots of 0.4, 0.8, 1.2, 1.6, 2.0, 2.4 ml were taken and diluted upto 10 ml with phosphate buffer pH 6.8 to get 4, 8, 12, 16, 20, 24 ppm for Tropisetron hydrochloride respectively. The absorbance was measured in the UV-spectrophotometer at 284 nm using phosphate buffer pH 6.8 as a blank and a graph of concentration versus absorbance was plotted.

Preparation of floating matrix tablets of Tropisetron

The primary ingredients involved in the matrix tablet include a hydrophilic polymer (HPMC, Sodium CMC), gas generating agent (Sodium carbonate), diluents (Spray dried lactose), lubricant (Magnesium Stearate), glidant (Talc). The quantity of ingredients used for various formulations is described in table 1.

The accurately weighed quantities of HPMC, sodium CMC and lactose were taken in a mortar and mixed uniformly. To this the required amount of Tropisetron was added and mixed properly. Sodium bicarbonate was added to the above blend and mixed thoroughly. The mixture was sieved through sieve number 22. This mixture was directly compressed on a single punch tablet machine using 10-mm standard flat-faced punch.

Evaluation of floating tablets (Jalonya et al., 2018)

The tablets were evaluated for in process and finished product quality control tests i.e. appearance, thickness, weight variation, hardness, friability, floating time, dissolution study.

Hardness

The hardness of the formulated tablets was tested using Monsanto type hardness tester. Three tablets from each batch of formulation were randomly taken and the force required to break the tablets was measured using hardness tester.

Friability

The friability test of the formulations was performed using a Roche type friability test apparatus. Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by the formula

$$\% \text{ Friability} = \frac{W_{initial} - W_{final}}{W_{initial}} X\ 100$$

Weight variation test

20 tablets were randomly taken and weighed to calculate the average weight of the tablets. Each of these tablets was individually weighed and the difference from average weight was calculated. The percent weight variation was calculated to determine the deviation from the average weight.

Thickness

The thickness of randomly selected tablets from each batch of formulation was measured using a digital vernier caliper.

Drug content

Five tablets from each formulation were weighed to determine the average weight. These tablets were crushed in a mortar then the amount of powder equivalent to 10 mg of drug was dissolved in phosphate buffer pH 6.8 and volume was made up to 100 ml using phosphate buffer. 10ml of the filtrate was made up to 100ml with phosphate buffer pH 6.8. 10µg/ml solution was prepared from the above solution and analyzed for drug content.

In vitro buoyancy studies

The tablets were placed in a beaker containing 250 ml of 0.1M HCl maintained at 37°C. The time required for the tablet to rise to the surface was determined as floating lag time and the time period up to which the tablet remained floating was determined as total floating time.

Floating Lag Time

The time taken by the tablet to emerge onto the surface of the liquid after adding to the dissolution medium at pH 1.2, temperature 37 ± 0.5˚C, paddle rotation at 50 rpm is observed.

Total Floating Time

The time for which the tablet floats constantly on the surface of the gastric fluid , at pH 1.2, temperature 37 ± 0.5˚C, paddle rotation at 50 rpm.

Swelling Index

One tablet from each formulation was kept in a Petri dish containing phosphate buffer pH 7.2. At the end of 2 h, the tablet was with-

drawn, kept on tissue paper and weighed. The weighing was continued for every 2 hr, till the end of 12 h. The % weight gain by the tablet was calculated by formula

$$S.I = \frac{Mt - Mo}{Mo} * 100$$

Where, S.I = swelling index, M_t = weight of tablet at the time (t) and M_0 = weight of tablet at time 0.

In-vitro dissolution

The USP type II paddle apparatus with a paddle speed of 50 rpm was used for dissolution testing for the formulated matrix tablets. The dissolution media used consisted of 900 mL of 0.1 N HCl and distilled water. 5 mL of samples were collected at time points of every hour until 12 h and the media was replenished with the same volume of fresh media. The free drug concentration was estimated using a UV spectrophotometer at a wavelength of 284 nm by suitable dilution with phosphate buffer pH 6.8.

Results and Discussion

Preformulation Studies

The preformulation studies form an essential part of the delivery system preparation. The results of the preformulation studies are presented in table 2.

These parameters confirm the purity of the drug.

Calibration curve of Tropisetron

Calibration curve of Tropisetron was determined by plotting absorbance versus concentration (µg/ml) at 284 nm.

The linear regression analysis for the calibration curve was Abs = 0.057(conc) – 0.004 with a regression coefficient of 0.999 (figure 1).

Drug-polymer compatibility study

The FTIR spectra of the pure drug and physical mixture of drug and excipient were recorded in between 400-4000 wave number (cm-1). Deletion of the peaks of the pure drug in the mixture spectra is usually taken as an indication of incompatibility of the drug and excipients. On comparison of the FTIR spectra of the drug and the mixture it was observed that no peak was deleted and only the intensities of the existing peaks changed which might be due to the coupling of absorption frequencies. This provides an evidence of compatibility between the drug and the matrix forming polymers.

Evaluation of matrix tablets

The tablets were evaluated for appearance, thickness, hardness, weight variation, friability, swelling index, in vitro buoyancy and dissolution study (Table 3).

The thickness of all formulation was ranged in between 4.8 to 4.9 mm. Hardness of tablet of all formulation ranged from 5.2 kg/cm^2 and 5.6 kg/cm^2. The hardness of all formulation showed variation because of formulation combination and powder properties. The friability of all formulation was in the range of 0.37% to 0.51%. All formulation exhibited less than 1% friability and hence passed the test for friability. The weight variation of all formulation was in the range of 1.8 to 4.2 %.

The *in vitro* buoyancy study suggests that all the formulations were able to float on the surface of the medium for more than 12 sec. The time required to reach the surface (lag time or float latency) was highest in HPMC containing formulations and was concentration dependent. Formulation F3 exhibited the highest lag time. On the other hand, the float latency was less in sodium CMC containing formulations as well as in the mix polymer formulation (F7).

Swelling study was performed on all the formulation for 12 h (figure 2). The swelling of HPMC containing formulations was slow and remained upto higher duration whereas the formulations containing sodium CMC exhibited a quick swelling which started to decrease from 8th hour of study. It was therefore concluded that the formulation F3 with 82.56% swelling at

the end of 12th hour was most effective in sustaining the drug release.

The dissolution study was done in 0.1M HCl medium to check the release control profile of the matrix. It was observed that the formulations F1, F2 and F3 could maintain the drug release upto 9, 11 and 12 hours respectively whereas formulations F4-F7 could not sustain the drug release with all drug released by 7 hours (figure 3).

Conclusion

The results obtained from the study conclusively indicate that use of HPMC as the hydrophilic polymer to absorb water and sodium bicarbonate as the gas generating agnet could help in achieving sustained release over a longer duration by assisting floating capacity and helps in reducing the dose as well as frequency of administration of the medicaments. Further *in vivo* release studies are needed to support for the conclusion of the present investigation.

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Table 1 Formula for matrix tablet preparation

Ingredient	Amount Used						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Tropisetron (mg)	5	5	5	5	5	5	5
HPMC K15 (mg)	75	100	125	-	-	-	50
Sodium CMC (mg)	-	-	-	75	100	125	50
Sodium Bicarbonate (mg)	50	50	50	50	50	50	50
Lactose (mg)	167	142	117	167	142	117	142
Magnesium Stearate (mg)	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc (mg)	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total Weight (mg)	300	300	300	300	300	300	300

Table 2. Preformulation parameters of Tropisetron

Parameter	**Observation**
Color	White
Odor	Odorless
Taste	Bitter
Appearance	Crystalline
Solubility	Freely soluble in 0.1N HCl, water; slightly soluble in ethanol and methanol
Melting Point	201-204°C
Loss on Drying	0.21%

Table 3. Quality parameters of matrix tablets of Tropisetron

Formula-tion code	Thickness (mm)	Hardness (Kg/cm2)	Weight variation (%)	Friability (%)	Drug con-tent (%)	Lag Time (sec)	Float Time (sec)
F1	4.8	5.2	1.8	0.39	98.9	65	>12
F2	4.9	5.3	2.3	0.37	97.4	68	>12
F3	4.9	5.5	2.1	0.42	99.2	72	>12
F4	4.8	5.6	3.6	0.38	97.9	42	>12
F5	4.9	5.3	4.1	0.46	98.7	45	>12
F6	4.9	5.5	2.9	0.51	99	49	>12
F7	4.8	5.6	3.4	0.49	99.2	52	>12

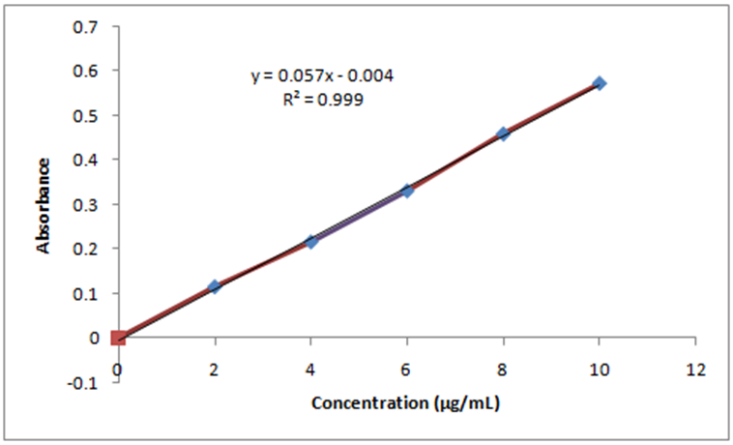

Figure 1. Calibration curve of tropisetron

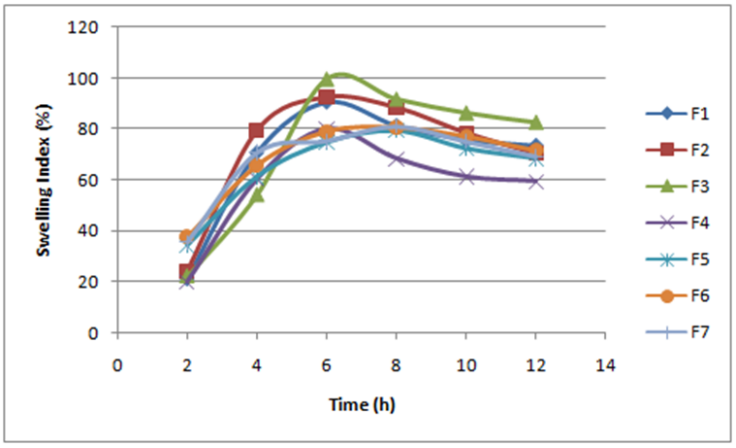

Figure 2. Swelling behaviors of floating formulations

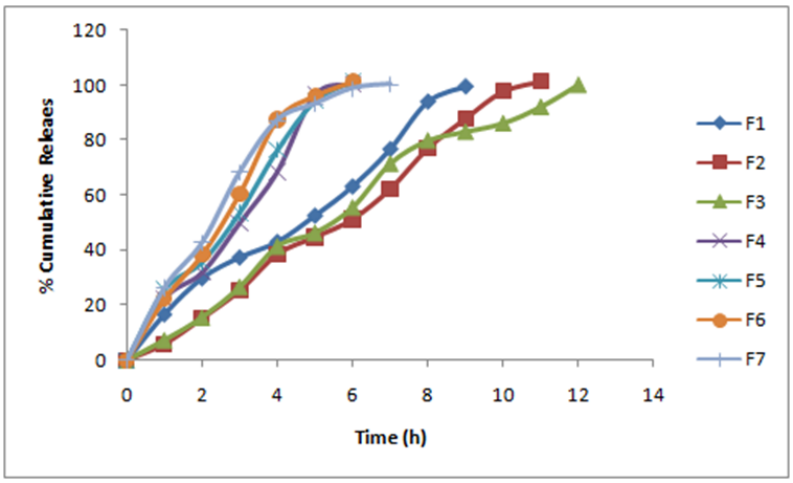

Figure 3. Release of Tropisetron from floating tablets

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