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Formulation and Evaluation of Sugar Spheres Containing Antiemetic Drug

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ABSTRACT

The aim of the research study was to formulate and evaluate Metoclopramide loaded sugar spheres for oral drug delivery. Sugar spheres were prepared by extrusion-spheronization method. Drug-excipients characterization studies were done by FTIR and UV analysis. Formulations were subjected to various evaluation parameters such as particle size, SEM (Scanning Electron Microscopy), drug content and *in vitro* drug release studies. Anti-emetic study was carried out by using rat model. Surface morphology of sugar spheres by SEM, showed it was spherical. Drug content was found to be 93.7%. The results of *in vitro* drug release data of the optimized sugar spheres formulation F8 showed drug release up to 98%. From the animal study, it was observed that F8 formulation showed better antiemetic activity. Stability studies were carried out for F8 formulation, revealed that there were no noticeable changes in drug content and *in vitro* drug release study. Hence, it is suitable candidate for the treatment of emesis, special focus on pediatrics.

Keywords: Sugar spheres, metoclopramide, emesis, extrusion-spheronization

INTRODUCTION

Metoclopramide is an antiemetic drug which is substituted benzamide and a derivative of para-amino benzoic acid (PABA), is structurally related to procainamide. The available marketed Metoclopramide dosage form is in liquid form are undergoing hydrolysis and oxidation slowly, which decreases the shelf life of the product. Hence it would be beneficial to improve the patient compliance and enhance the oral solubility of Metoclopramide by sugar spheres or pellets, which

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would in turn lead to probable improvement in the bioavailability of the drug[1-3]. Pellets are the aggregates of granules or fine powder mixture of drug and excipients; they are small spherical or semi spherical free flowing solid units ranging from 0.5 to 3 mm, which are usually used for oral administration. The pellets are usually compressed into tablets or filled into hard gelatin capsules, they are usually formulated as immediate release or sustained release dosage forms, and they can also be coated to target a particular site for its action[4]. Extrusion-Spheronization is a multistep process, the advantage of this method is to fabricate the spheres with high drug loading i.e.; up to 90%. This process involves the dry mixing of the drug and excipients to achieve a homogenous mixture, then followed by wet massing of the dry mixture, then it is granulated, extrusion of the wet mass is carried out where noodle like extrudates are obtained, then this mass is transferred into the spheronizer which produces the spherules, then these spherules are dried in dryer followed by screening is done to obtain a required particle size. This process is called as mass extrusion-spheronization[4, 5]. Our present work is to formulate and evaluate sugar spheres containing antiemetic drug for paediatric administration as conventionally available formulation for pediatrics' are liquid dosage form. These formulations undergo oxidative and hydrolytic degradation. It has less bioavailability, as it undergoes first pass metabolism. Therefore, to overcome these problems mouth dissolving sugar spheres loaded with Metoclopramide was formulated. The main objective of the research work was to formulate and evaluate sugar spheres containing antiemetic drug for treatment of emesis [6-8.]

METHODOLOGY

Metoclopramide were procured from All-well Pharmaceuticals Chandigarh India, β-Cyclodextrin and other excipients from CDH Bengaluru, India. Other solvents and chemicals are analytical grades.

Preformulation study

A preformulation study was useful to identify the Metoclopramide drug and studied the compatibility studies with the excipients. Preliminary solubility studies were carried out for known quantity of drug with different solvents. Melting point of drug was determined by using Thiele tube apparatus. Determination of λ_{max} was analyzed using UV spectrophotometer using phosphate buffer pH 6.8. Calibration curve was constructed using phosphate buffer pH 6.8, after suitable dilutions absorbance was taken using UV visible spectrophotometer at 240 nm[9, 10].

Drug-excipient Compatibility Studies (FTIR)

Metoclopramide was placed in the sample port of FTIR; the spectrum of Metoclopramide was recorded. Compatibility studies were carried out to know the possible interactions between Metoclopramide and β- cyclodextrin, Drug: β-cyclodextrin complex with 1: 4 ratio was considered to know the interactions, based on high drug loading capacity[11].

Preparation of Metoclopramide complex with β-Cyclodextrin (β-CD) by Kneading Method

Metoclopramide and β-cyclodextrin in molar ratios of 1:1, 1:2, 1:3 and 1:4 were taken in mortar and pestle, and then wetted with appropriate quantity of IPA to obtain a paste. All 1:1, 1:2, 1:3 and 1:4 molar ratios were then subjected to kneading by trituration for 30 min. After that it was dried at 50°C, crushed, sieved and stored at temperature of 25±2.0°C and relative humidity between 40-50% RH[12-14].

Preparation of Metoclopramide sugar spheres by Extrusion-Spheronization method

Formulation chart was prepared by using drug-complex with different ratios of disintegrants & other excipients in F1-F9 formulations as shown in the Table 1. Extrusion-Spheronization are a multistage process for obtaining pellets with uniform size from wet mass using non-aqueous solvents. The method involves the following steps. The dry mixing of the drug and excipients, in order to achieve homogenous powder dispersions[15-18]. The powder mixture was wet mixed with IPA as a solvent to form a sufficiently damp mass. In extrusion stage, the wet mass is converted into cylindrical segments with a uniform diameter of 3 mm at 50 rpm. In spheronization stage, the small cylinders are rolled into solid spheres (spheroids) at 500 rpm. The drying of the spheroids at 45°C in order to achieve the desired final moisture content. Screening (optional), to achieve the desired narrow size distribution [19-23].

Table1: Formulation chart of Sugar spheres containing Metoclopramide

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug complex (1:4) g	8.02	8.02	8.02	8.02	8.02	8.02	8.02	8.02	8.02
Sucrose (g)	58.98	56.98	54.98	52.98	50.98	55.98	52.98	49.98	46.98
MCC (g)	30	30	30	30	30	30	30	30	30
Sodium starch glycolate (%)	0	2	4	6	8	-	-	-	-
Cross carmellose sodium (%)	-	-	-	-	-	3	6	9	12
Preservatives (%)	1	1	1	1	1	1	1	1	1
Methyl cellulose (%)	2	2	2	2	2	2	2	2	2
IPA	QS	QS	QS	QS	QS	QS	QS	QS	QS
Flavor (Vanillin)	QS	QS	QS	QS	QS	QS	QS	QS	QS
Color	QS	QS	QS	QS	QS	QS	QS	QS	QS
Batch size	100 g								

EVALUATION OF SUGAR SPHERES

Physicochemical characteristics of pellets[24]:

The porosity, compressibility and density of prepared pellets were defined by bulk density (BD), tapped density (TD) and porosity was determined by using digital density apparatus (Innovative XCN 77). In density apparatus about 10 g of pellets were added into a 100 mL calibrated measuring cylinder. The initial volume (bulk volume) is noted down. After 100 tapping further final volume were noted, the following equations were used for calculating the BD and TD. Then, flow properties were calculated by using Hausner's ratio formulas given below.

$$\text{B}ulk\ Density = Weight\ of\ pellets/Bulk\ volume$$

$$Tapped\ density = Weight\ of\ pellets/(Tapped\ volume)$$

$$Porosity = Volume\ of\ voids/Total\ volume$$

$$Hausner's\ ratio = Bulk\ density/Tapped\ density$$

Angle of repose[24]

The angle of repose was calculated using the fixed funnel method. The pellets, were measured exactly weight equivalent to 10 g, had been transferred to the funnel. The funnel height was set in such a way that the funnel tip reached the heap apex of the pellets. The pellet was allowed to flow through the funnel freely on to the surface. Finally, the diameter of pellets cone was measured. The angle of repose was calculated using following formula.

$$Angle\ of\ repose\ (\theta) = tan - 1h/r$$

Where, *'h'* and *'r'* are height and radius of the pellet cone.

Friability

Friability of the pellets was performed by using USP Roche friabilator (FE2, Electro lab, Mumbai India). Pre-weighed about 5 g pellets were placed in the plastic chamber, along with pellets around 10 g of glass pellets were added to increase the stress level pellets. It was then operated for 100 revolutions. Pellets were dropping from a distance of six inches with each revolution, after completion of desired cycles; pellets were removed from friabilator, dusted and % friability was calculated by using formula [24].

$$\%\ Friability = Initial\ weights\ of\ pellets - Final\ weight\ of\ pellets/Initial\ Weight\ of\ pellets \times 100$$

Particle size: Particle size was determined by using sieve analysis using sieve shaker machine.

Drug Content [24]

About 10 g of pellets were crushed and powdered. Weighed accurately the quantity equivalent to 5 mg of drug and taken in 10 mL volumetric flask and volume was made up to the mark with phosphate buffer pH 6.8 and filtered through 0.45 µm Whatman filter paper and 1mL of this solution was taken and volume made up to 10 mL of phosphate buffer pH 6.8. The absorbance was measured at 240 nm using UV Spectrophotometer (Shimadzu 1800, Japan). Percentage drug content is calculated by using formula.

$$Drug\ content = Concentration \times Dilution\ factor$$

$$\%Drug\ content = Drug\ content(mg)/Label\ Claim\ (mg)$$

Disintegration test [25, 26, 27]

Disintegration test was performed using disintegration tester (USP) (Electrolab, ED 2L, India). About 1 g of pellets were weighed and placed in all the 6 tubes and the disc was placed at the top, the beaker was filled with phosphate buffer pH 6.8 solution, the disintegration was carried out and the bath temperature was maintained at 37±2°C. Disintegration time was recorded. The pellets were considered to be completely disintegrated as no residue remains on the screen.

Scanning electron microscopy

Scanning electron microscope, it produces images of samples by scanning it with focused beam of electrons. The electrons interact with atoms in the sample, producing various signals that can be detected and that contain information about the samples surface topography. SEM photographs were taken for the prepared sugar spheres using a scanning electron microscope (Carl Zeiss FESEM model number: ULTRA 55 USA), at room temperature. The photographs were observed for morphological characteristics. Photographs were taken at the magnifications of 22.00 X and 38.00 X[25].

In vitro drug release studies

Dose equivalent to 5 mg of drug containing Metoclopramide pellets using USP 29 type I apparatus (Dissolution Tester EDT 08Lx, Electrolab, Mumbai, India) stirred at speed of 50 rpm in 900 mL of phosphate buffer pH 6.8 at 37±0.5°C. About 1 mL sample was withdrawn at predetermined time intervals and it was replaced with fresh dissolution media to maintain the sink condition. The withdrawn sample were filtered through 0.45 µm membrane filter and the volume was made up to 10 mL using volumetric flask and analyzed the absorbance periodically by using UV spectrophotometer (UV1700, Shimadzu, Japan) at 240 nm[25].

Antiemetic activity in rat model

The experimental protocol for the antiemetic activity was approved by Institutional Animal Ethical Committee IAEC/ABMRCP/2019-2020/5. Antiemetic activity was carried out using 8 female rats as they are more sensitive compared to male rats. Each rat weighing between 200-250 g were selected. Animals were divided into 3 groups. Out of 3 groups, 3 animals in emetic group, 3 animals in antiemetic group and 2 animals in control group. Kaolin pellets and saccharine solution were placed on the stainless-steel grid cover of the cage for 6 days prior to 5-flurouracil to allow the rats to adopt to its presence. All the animals were given oral administration of physiological saline for 3 days (dosage 2 mL/day) prior to administration of the 5-flurouracil. On 4th and 5th day, for Metoclopramide group, Metoclopramide solution (0.45 mg/kg body weight; dosage

0.5 mL/day), given through oral administration, whereas the other 2 groups continued to receive physiological saline. On the 7th day, 5-flurouracil (0.2 mL through oral route) was administered to all rats, except blank group. After 1 hour subsequent to the oral administration, Metoclopramide was administrated to emetic group. The kaolin, saccharin solution and normal feed containers were removed each day (at 10 am). The kaolin and normal feed were collected and weighed, and the weight of the bottle of saccharin was also being determined. The quantity of kaolin, normal feed and saccharin solution consumed during each 24 h period was determined by the weights with the initial weights[28].

The following formula was used to determine the ultimate weight value. Ultimate weight value (day n) = weight (day n) – weight (day n+1)

Stability studies

The optimized formulation was kept in the foil sachet and sealed tightly and kept in stability chamber (Thermo lab, scientific equipment's Ltd) maintained accelerated stability condition at temperature 40±2°C / 75±5% RH for 6 months. At at the intervals of every 3 months, samples were analyzed for drug content, disintegration time and *in vitro* drug release studies[24].

RESULTS and DISCUSSION

The preliminary solubility of Metoclopramide was found that, drug was soluble in ethanol, chloroform, benzene, 1 M HCl, sparingly soluble in methanol, DCM, DMSO, acetone, 0.5 N NaOH, Metaclopramide hydrochloride is freely soluble in Water and phosphate buffer pH 6.8[9],[10,29]. The melting point of Metoclopramide was determined by using Thiele tube method and was found to be in the range of 149-155°C, which complied with European pharmacopoeia standards, thus indicating purity of obtained Metoclopramide sample [9, 10].

The position of peak in FTIR spectrum of pure Metoclopramide is compared with those in FTIR spectrum of Metoclopramide with β-cyclodextrin. The pure drug Metoclopramide peak at 686 cm^{-1} due to Cl bending, 3397 cm^{-1} due to N-H stretching, 1835 cm^{-1} due to C=O stretching, 1590 cm^{-1} due to C=C stretching, 2289 cm^{-1} due to CN stretching, 2763 cm^{-1} due to OCH stretching these are the characteristic peaks of Metoclopramide. It was observed that, there was drug characteristic peaks were observed as shown in the Figure 1a & Figure 1b, which proved that drug and β-cyclodextrin were compatible. The drug release profile for drug complex of all formulations 1:1-1:4 was found to be ranging between 52.7±3.95 to 83.1±7.49%. The results were shown in Figure 2. It was found that the 1:4 ratios showed the better drug release compared to other formulations. Hence it was selected for the formulation of sugar spheres[11, 30].

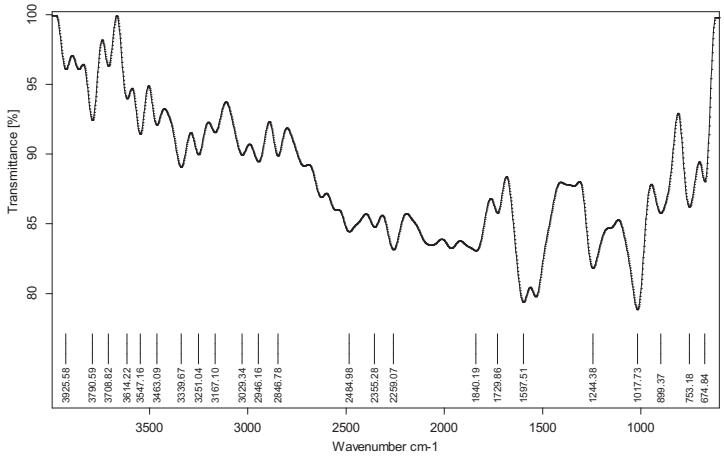

Figure 1a. FTIR Spectrum of Metaclopramide

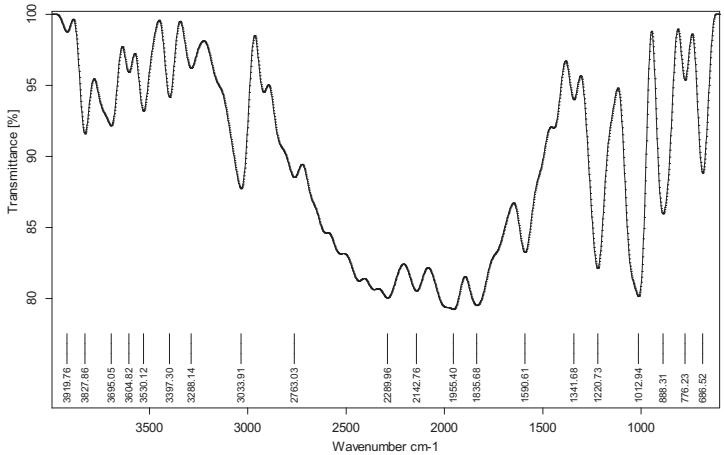

Figure 1b. FTIR spectrum of Metaclopramide with β-Cyclodextrin

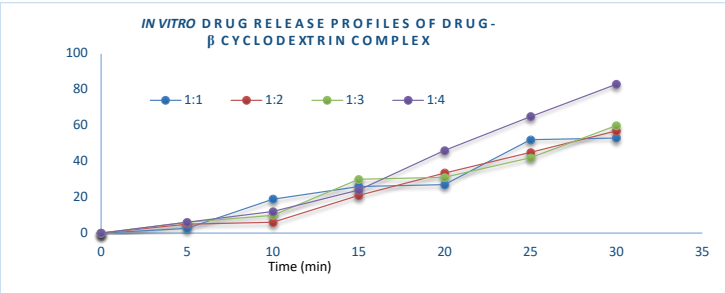

Figure 2. *In vitro* drug release profiles of Metoclopramide drug complex with β- Cyclodextrin (β-CD) by Kneading Method

Evaluation parameters of sugar spheres:

The pellets were tested for bulk density, tapped density, Carr's index, Hauser's ratio, porosity and angle of repose. The angle of repose in F4 to F5 formulations ranges from 26.5±2.05 to 30.11±0.78 i.e. in the normal limits gives excellent flow ability, pellets are free flowing, and it had been compliance with IP standards. Porosity of all batches ranges from 81.2±3.84 to 96.1±2.26%. The bulk density and tapped density ranges from 0.38±0.04 to 0.62±0.03 (g/mL) and 0.4±0.04 to 0.76±0.06 (g/mL) respectively, which is in normal range shows good flow ability. Hausner's ratios of all batches were in normal range i.e. 1.04±0.10-1.23±0.09, shows excellent flowing ability. The resulting values shows good flowability as specified in the Table 2. All formulation batches were evaluated for friability testing in triplicates. Formulations F5-F9 shows the friability 0-0.2%, its well, within the limit, however, the friability values greater in F1 to F4 as shown in the Table 3. The results of friability indicated that the pellets formulations were mechanically stable. Disintegration time of all formulations was performed using USP disintegration test apparatus, temperature at 37±°C using phosphate buffer pH 6.8. Formulated products showing very less disintegrating time, i.e.193-480 seconds. Disintegration is depending abreast on the concentration of disintegrants[31] and when cross carmellose sodium concentration increases the disintegration time was at faster rate, In case of F5 formulation disintegration time was faster, due to sodium starch glycolate concentration was more. Formulations F8 was disintegrated within 193 sec, better disintegration rate when compared to all other formulations. The values of disintegration time were shown in Table 3. Drug loading was found to be 49.2-93.7%, highest percentage was observed in F8, where cross carmellose sodium high concentration was utilized in the formulation, Cross carmellose sodium having high water uptake and swelling characteristics due to the presence of carboxymethyl sodium substituents[32]. The average particle size was found to be 1.0±0.01 to 1.0±0.02 mm. The scanning microscopy (SEM) analysis is vital for determining the surface morphology, size, and shape. SEM images of the formulated F8 pellets at different magnification were as shown in Figure 3, Surface morphology of pellets studied by SEM, indicated that the pellets were spherical shaped with rigid surface and were discrete, isolated images observed from SEM, predicted that pellets are free flowing, and number of micro porous surface structure was observed.

Table 2: Flow properties of pellets

Formulations	Angle of repose (ɵ) Mean±SD *	Bulk density (g/mL) Mean±SD *	Tapped density (g/mL) Mean±SD *	Hausner's ratio (%) Mean±SD *	Porosity (%) Mean±SD *
F1	11.3±1.10	0.55±0.03	0.62±0.10	1.12±0.06	88.8±2.80
F2	5.71±1.73	0.38±0.04	0.4±0.04	1.04±0.10	96.1±2.26
F3	20.8±0.98	0.58±0.10	0.66±0.07	1.13±0.07	88.2±2.26
F4	26.5±2.05	0.55±0.06	0.62±0.10	1.12±0.13	88.8±1.41
F5	25.6±2.22	0.52±0.04	0.55±0.05	1.05±0.04	94.7±2.81
F6	27.9±0.69	0.55±0.05	0.58±0.16	1.05±0.17	94.4±1.80
F7	28.8±0.83	0.52±0.06	0.58±0.07	1.11±0.13	89.4±5.71
F8	30.1±0.78	0.62±0.03	0.76±0.06	1.23±0.09	81.2±3.84
F9	28.4±1.49	0.45±0.09	0.5±0.06	1.10±0.09	90.9±1.49

*n=3 Mean±SD

Table 3: Physicochemical parameters for prepared pellets

Formulation code	Avg Particle size (mm)	Friability (%) Mean±SD*	Disintegration time (sec) Mean±SD*	Drug content (%)
F1	1.0±0.01	2.9 ±0.35	480sec ±0.40	49.2
F2	1.0±0.02	1.7 ±0.28	399sec ±0.57	58.8
F3	1.0±0.01	1.2 ±0.21	326sec ±0.76	78.6
F4	1.0±0.01	10.2 ±0.76	258sec ±0.64	77.2
F5	1.0±0.01	0.1 ±0.04	256 sec ±1.70	76.4
F6	1.0±0.01	0 ±0.04	371 sec ±0.38	83.0
F7	1.0±0.02	0.2 ±0.17	247sec ±0.36	83.1
F8	1.0±0.01	0 ±0.04	193sec ±0.38	93.7
F9	1.0±0.01	0 ±0.04	194sec ±0.48	91.6

*n=3 Mean±SD

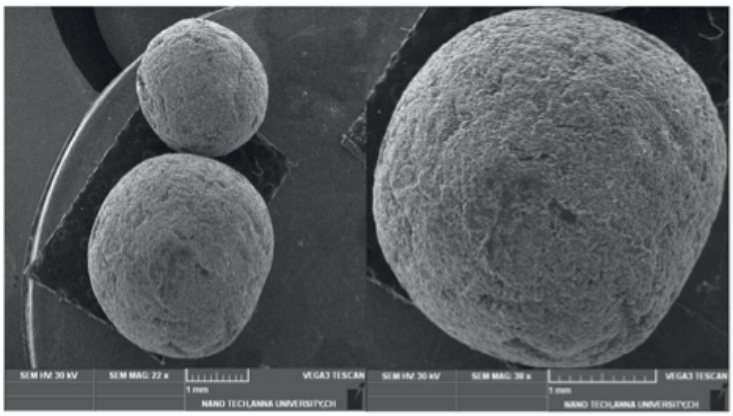

Figure 3: SEM Photograph of F8 magnification at 22.00 X & 38.00 X

In vitro drug release profiles:

In vitro drug release study was carried out for 30 min for formulation F1-F9. The amount of drug released at the end of 30 min is varying from 69.77 to 98.13%. The formulations contain 2-8% of sodium starch glycolate and 3-12% of cross carmellose sodium. The results of *in vitro* drug released were found to be lowest 69.77% in F1 formulation, which contained 2% sodium starch glycolate and the highest 98.13% drug released in F8 formulation, which contained 9% cross carmellose sodium. Sodium starch glycolate and Cross carmellose sodium are superdisintegrants which helps in faster disintegration followed by drug release from the pellets. Overall F8 formulation showed the optimum results. The results were as shown in the Figure 4.

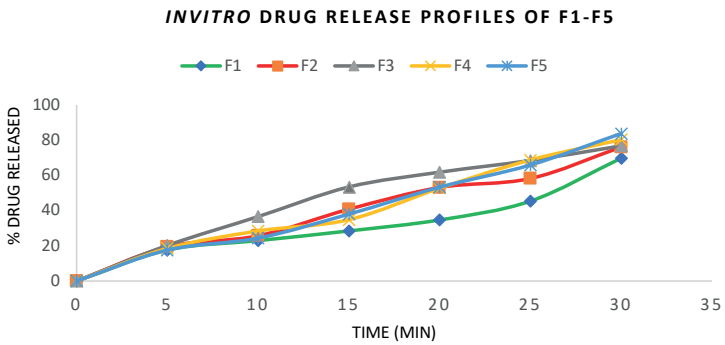

Figure 4a. *In vitro* drug release profiles of F1-F5

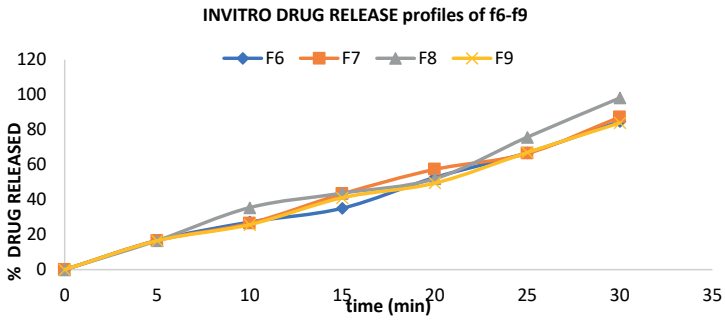

Figure 4b. *In vitro* drug release profiles of F6-F9

Anti-emetic studies using rat model:

Anti-cancer drug 5-fluorouracil unwanted side effect is severe emesis. According to American Society of Clinical oncology guidelines, 5-Fluorouracil causes acute and chronic emesis. Delayed vomiting occurs after 24 h, it persists for a week. In contrast to rodent species possess an emetic reflex, rat's exhibits pica behavior to stimuli that induce emesis. Nonnutritive substance such as Kaolin is a phenomena of emetic reflux[28].

From the animal study it was observed that kaolin consumption was apparently enhanced 1st day which indicated that the rats showed the pica behavior, whereas after Metoclopramide administration, initially till 24 h; 2.08±082 g kaolin consumption from the rat group was observed, followed by after 48 h Kaolin consumption was gradually decreases to 0.82 ±0.62 g, after 72 h still decreases to 0.43±0.72 g as shown in the Table 4.

In case of Sacharin solution, after 24 h, consumption with blank was 35.46±0.34 mL, with Control Saccharin solution consumption was 20.26±10.56 mL, followed by with Metoclopramide 28.66±0.65 mL, it was gradually decreased to 24.63±0.86 mL (*Mean ± SEM n=3/group) after 72 h of study.

On normal feed consumption induced by administration of 5-Flurouracil in rats was studied. With control consumption of feed was 8.19±0.87 g, it was gradually decreased to 6.63±0.96 g after 72 h of study. On Metaclopramide administration rat group feed consumption on 1st day was 9.24±0.45 g was consumed by the rats, followed by on 3rd day, gradually food intake was increased to 10.61±0.57 g. By the above observation it was concluded that F8 formulations the antiemetic activity. The results were tabulated in the Table 4-6.

Table 4. Kaolin consumption induced by administration of 5 fluorouracil in rats

Kaolin consumption (g)				
Group	n	0-24 h	24-48 h	48-72 h
Blank	2	0.58±0.22	0.36±0.14	0.49±0.72
Control	3	3.65 ±0.92	0.84 ±0.52	0.53±0.82
Metoclopramide	3	2.08±0.82	0.82 ±0.62	0.43±0.72

*Mean ± SEM (Standard Error Mean)

Table 6. Normal feed consumption induced by administration of 5 fluorouracil in rats

Normal feed consumption (g)				
Group	n	0-24 h	24-48 h	48-72 h
Blank	2	20.61±0.65	22.48±0.98	20.33±0.78
Control	3	8.19±0.87	5.76±0.74	6.63±0.96
Metoclopramide	3	9.24±0.45	10.07±0.86	10.61±0.57

*Mean ± SEM (SEM= Standard Error Mean

Stability studies:

The most satisfactory formulation F8 was stored in sealed sachets of aluminum foil. Then the formulation was exposed to 40±5°C and 75% RH using stability chamber. At the end of one month sample were evaluated for Disintegration time was found to be 3 mins 33 sec and drug content was found to be 93.9%, which confirmed that there was no much differences between the initial values and the result obtained during stability studies, thus indicating stability of prepared formulation is stable. The results were tabulated in Table 5. The formulation F8 After one month of stability study, there was no considerable changes in *in vitro* drug release studies were observed, and showed a drug release of 97.77±1.23% (*n=3 Mean± SD). The results were shown in the Table 7 and Figure 5. Formulation F8 shows better % CDR, disintegration time and drug content, so it was selected. We conclude that formulated Metoclopramide loaded sugar spheres F8, had good stability and better oral solubility of drug which enhances the bioavailability of the drug in systemic circulation, so it is suitable paediatric formulation for the treatment of emesis to enhance better absorption of drug through oral route.

Table 5. Saccharin solution consumption induced by administration of 5 fluorouracil in rats

Saccharin solution consumption (ml)				
Group	n	0-24 h	24-48 h	48-72 h
Blank	2	35.46± 0.34	34.63±0.65	31.28±0.76
Control	3	20.26±10.56	19.32±0.67	26.98±0.65
Metoclopramide	3	28.66±0.65	25.57±0.67	24.63±0.86

*Mean ± SEM (SEM=Standard Error Mean)

Table 7. Evaluation parameters of F8 after 1 month of stability study

Days	Stability condition	Drug content (%)	Disintegration time (sec)*
0	40±2°C,75±5% RH	93.7	193±0.38
15	40±2°C,75±5% RH	92.5	183±0.41
30	40±2°C,75±5% RH	93.9	213±0.34

*n=3 Mean± SD

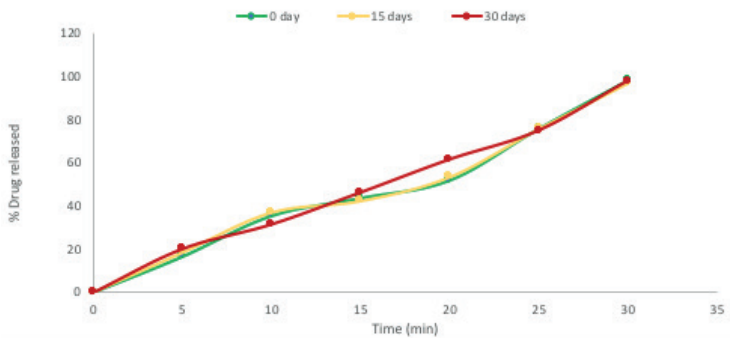

Figure 5. Drug released profiles of F8 formulation after 1 month stability study

DECLARATION OF INTERESTS

Authors declare no conflict of interest.

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