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FORMULATION AND CHARACTERIZATION OF MECLIZINE FLOATING GASTRORETENTIVE TABLETS USING SOME SYNTHETIC AND NATURAL POLYMERS

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Abstract:
Gastroretentive drug delivery system (GRDDS) is one of the novel approach in this area. Oral controlled release dosage forms are the most commonly formulated but still offer highest attention in the area of novel drug delivery systems. Meclizine hydrochloride (MCZ) is a first-generation antihistamine of the piperazine class drug, used in the treatment of motion sickness (H_1 receptor antagonist). Meclizine is a white to light yellowish-white crystalline powder and practically insoluble in water. Meclizine has a plasma elimination half-life of about 5-6 hours in humans and dose 12.5-50 mg PO given 1 hour before travel. The aim of present work to formulate and characterize sustain release gastro-retentive floating tablets of Meclizine hydrochloride using some synthetics and natural polymers like HPMCK4, HPMC K15, PVP K30, guar gum or Gum tragacanth. The % drug content of all the formulated tablets were found within the limit. % drug content value of Meclizine was within 98.12±0.45% to 99.45±0.32%.The results within the range indicate uniform of mixing. The in vitro drug release was carried out for formulation (F1, F2, F3, F4, F5, F6, F7 and F9 Formulation and release kinetics was calculated for optimized formulation F7. When the regression coefficient values of were compared, it was observed that 'r^2' values of first order was maximum i.e. 0.980 hence indicating drug release from formulations was found to follow First order release kinetics.

Keywords: *Gastroretentive drug delivery system, Meclizine hydrochloride, Synthetic and Natural Polymers*

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INTRODUCTION:

Gastroretentive drug delivery system (GRDDS) is one of the novel approaches in this area. Oral controlled release dosage forms are the most commonly formulated but still offer highest attention in the area of novel drug delivery systems [2].Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation,the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the GIT [3]. Poor absorption of many drugs in the lower GIT necessitates controlled release dosage forms to be maintained in the upper GI tract, particularly the stomach and upper small intestine [4].These drug delivery systems suffer from mainly two adversities: the short gastric retention time(GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine)leading to diminished efficacy of administered dose [5].To formulate a site-specific orally administered controlled release dosage form, itis desirable to achieve a prolong gastric residence time by the drug delivery.

FDDS is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability [6]. This system is desirable for drugs with an absorption window in the stomach or in the upper small intestine [7].This have a less density then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuation in plasma drug concentration.

Meclizine hydrochloride (MCZ) is a first-generation antihistamine of the piperazine class drug, used in the treatment of motion sickness (H1 receptor antagonist). Meclizine is a white to light yellowish-white crystalline powder and practically insoluble in water.

Meclizine has a plasma elimination half-life of about 5-6 hours in humans and dose 12.5-50 mg PO given 1 hour before travel. The aim of present work to formulate and characterize sustain release gastro-retentive floating tablets of Meclizine hydrochloride using some synthetics and natural polymers like HPMCK4, HPMC K15, PVP K30, Guar gum or Gum tragacanth.

MATERIAL AND METHODS:

Method for preparation of Meclizine floating gastroretentive (FGR) tablets:

Direct compression was taken after to manufacture the gas generating floating tablets of Meclizine[8]. Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, and F9) were set up by direct compression. Every one of the polymers chose, drug and excipients were gone through strainer no. 40 preceding utilizing into plan. The sum and proportion of drug and polymers were weighed according to given in table no. 1 and all the definition were utilized for encourage assessments parameters.

Optimization of gastro retentive floating tablets of Meclizine:

Optimization of formulation carried out on the basis of OVAT (One variable at time) using amount of excipient used like Excipients like HPMC K4, HPMC K15 and PVP K30.

Table 1: Various formulations of Meclizine gastroretentive tablets

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Meclizine	25	25	25	25	25	25	25	25	25
HPMC K4	100	120	140	-	-	-	50	60	70
HPMC K15	-	-	-	100	120	140	50	60	70
PVP K30	-	-	-	-	-	-	20	20	20
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)_2$	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Lactose	135	115	95	135	115	95	115	95	75
Total Weight	300	300	300	300	300	300	300	300	300

Evaluation of Precompression Parameter [9-10]

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of powder}}{\text{Volume of Packing}}$$

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of powder}}{\text{Tapped Volume of Packing}}$$

Carr's Compressibility index:

Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

$$\text{Carr's Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \text{X } 100$$

Hausners ratio:

It is determined by comparing tapped density to the bulk density by using following equation:-

$$\text{Housner's ratio} = \frac{\text{Tapped bulk density}}{\text{Loose Bulk density}}$$

Hausner's ratio value <1.25 shows better flow properties

Evaluation of tablets:

All the tablets were evaluated for following various parameters which includes;

General Appearance:

Five tablets from various batches were randomly selected and organoleptic properties such as color, odor, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter:

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated [11].

Drug content:

Twenty tablets were taken and amount of drug present in each tablet was determined [84]. The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask. The powder was dissolved in 5 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ_{max} of 232 nm using of 0.1 N HCl as blank.

Hardness:

For each formulation, the hardness of five tablets was resolved utilizing the Monsanto hardness tester [12].

Friability:

The friability of a sample of 10 tablets was estimated utilizing a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated [13].

Uniformity of weight:

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

***In vitro* buoyancy studies:**

In vitro buoyancy was determined by floating lag time as per the method. The tablets were separately in a 100 ml glass beaker containing simulated gastric fluid, pH 1.2 as per USP. The time necessary for the tablet to increase to the outside and float was determined as floating lag time [14].

Dissolution rate studies:

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was set into the dissolution flask maintaining the temperature of 37±0.5°C and rpm of 75. One prepared Meclizine tablet was set in every container of dissolution

apparatus. The mechanical assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 10 hours using 10ml pipette. The new disintegration medium (37°C) was supplanted each time with a similar amount of the sample and takes the absorbance at 232nm using UV/Visible spectroscopy [15].

RESULTS AND DISCUSSION:

The thickness of the tablets was reported in the micrometer (mm).The thickness of tablet indicates that, die fill was uniform. The thickness depends on the size of the punches (8 mm) and the weight of one tablet (300mg). The value of thickness ranges between 3.11±0.05 to 3.13±0.02mm.

Friability determines the strength of the tablets. The friability for all the formulations was below 1% indicating that the friability was within the prescribed limits. The results of friability test indicate that the tablet possesses good mechanical strength. The friability value ranges from 0.625±0.047 to 0.865±0.014.

The mean hardness values were measured for all the formulation using Monsanto hardness tester. The hardness value ranges from 6.3±0.3 to 6.5±0.2kg/cm^2.

Twenty tablets were randomly selected from each formulation and evaluated. The obtained data were almost uniform. The values of tablets average weight ranging from 295±5 to 305±4 mg. All the tablets passed weight variation test as the % weight variation was within the USP Pharmacopoeia's limits of ±5% of the weight.

The % drug content of all the formulated tablets were found within the limit. % drug content value of Meclizine was within 98.12±0.45% to 99.45±0.32%.The results within the range indicate uniform of mixing.

Table 2: Result of pre-compression properties of Meclizine FGR (floating gastroretentive) tablets

Formulation Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.345	0.456	24.342	1.322
F2	0.352	0.462	23.810	1.313
F3	0.348	0.456	23.684	1.310
F4	0.349	0.453	22.958	1.298
F5	0.355	0.492	27.846	1.386
F6	0.347	0.458	24.236	1.320
F7	0.345	0.459	24.837	1.330
F8	0.347	0.458	24.236	1.320
F9	0.358	0.452	20.796	1.263

Table 3: Results of post compression properties of Meclizine FGR tablets

Formulation code	Thickness (mm)	Hardness (kg/cm2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3	Total floating duration (h)
F1	3.11±0.05	6.5±0.2	302±5	0.658±0.058	98.12±0.45	>12
F2	3.12±0.03	6.4±0.3	305±4	0.754±0.065	98.85±0.25	>12
F3	3.13±0.02	6.5±0.4	298±6	0.625±0.047	98.65±0.36	>12
F4	3.12±0.04	6.5±0.2	295±5	0.741±0.036	98.78±0.25	>12
F5	3.12±0.03	6.3±0.3	302±4	0.856±0.025	99.05±0.31	>12
F6	3.12±0.04	6.5±0.2	301±3	0.845±0.035	98.74±0.14	>12
F7	3.12±0.03	6.5±0.2	296±4	0.865±0.014	99.45±0.32	>12
F8	3.13±0.02	6.4±0.1	285±2	0.745±0.026	98.98±0.15	>12
F9	3.12±0.02	6.4±0.2	296±2	0.785±0.036	98.78±0.36	>12

Table 4: Results of *in-vitro* buoyancy study of Meclizine FGR Floating time

S. No.	Formulation Code	Floating lag times (sec)
1.	F1	58
2.	F2	52
3.	F3	49
4.	F4	48
5.	F5	45
6.	F6	42
7.	F7	36
8.	F8	45
9.	F9	47

Table 5: *In-vitro* drug release study of FGR tablets

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	35.65	33.32	32.25	32.32	30.25	29.85	23.36	19.98	16.65
1	48.85	46.65	42.32	45.65	43.32	43.32	35.65	25.65	20.23
1.5	65.85	63.32	58.85	63.32	62.12	55.65	45.56	36.65	26.65
2	79.98	75.56	69.98	78.85	75.65	65.45	65.58	48.85	35.45
3	98.85	86.65	75.56	92.25	88.85	75.65	68.85	55.69	48.85
4	-	98.78	85.65	99.12	95.45	85.56	75.65	69.98	59.98
6	-	-	98.85	-	98.85	96.65	85.65	78.85	69.98
8	-	-	-	-	-	98.15	92.23	86.65	76.65
12	-	-	-	-	-	-	98.85	92.23	83.32

Table 6: *In-vitro* drug release data for optimized formulation F7

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	23.36	1.368	76.64	1.884
1	1	0	35.65	1.552	64.35	1.809
1.5	1.225	0.176	45.56	1.659	54.44	1.736
2	1.414	0.301	65.58	1.817	34.42	1.537
3	1.732	0.477	68.85	1.838	31.15	1.493
4	2	0.602	75.65	1.879	24.35	1.386
6	2.449	0.778	85.65	1.933	14.35	1.157
8	2.828	0.903	92.23	1.965	7.77	0.890
12	3.464	1.079	98.85	1.995	1.15	0.061

Table 7: Regression analysis data of Meclizine floating tablets

Batch	Zero Order	First Order	Higuchi	Peppas
	R^2	R^2	R^2	R^2
F7	0.773	0.980	0.963	0.929

CONCLUSION:

The *in vitro* drug release was carried out for formulation (F1, F2, F3, F4, F5, F6, F7 and F9 Formulation and release kinetics was calculated for optimized formulation F7. When the regression coefficient values of were compared, it was observed that 'r^2' values of first order was maximum i.e. 0.980 hence indicating drug release from formulations was found to follow First order release kinetics. Further the optimized formulation F7 of gas generating floating tablet consist of Citric acid and HPMC K100 which results in desirable lag time, floating time and percent drug release. From the in vitro studies, it was also shows that there was an increase in the solubility.

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