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Formulation and Evaluation of Bilayered Floating Tablets of Metoclopramide HCL

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Abstract
The current controlled release technology made possible to release drugs at a constant release rate for longer periods of time ranging from days to years.
Objective: *The objective of the present work was to develop bilayer floating tablets of metoclopramide hydrochloride.*
Methods: *Metoclopramide Hydrochloride bilayer floating tablets were prepared by direct compression method. The tablet contains two layers one is floating layer and other is sustain release layer in which drug is incorporated. Nine formulations were prepared in which different polymers were used in different concentrations. Metoclopramide hydrochloride concentration was kept constant and the concentration of polymers such as HPMC K4M, HPMC K15M, HPMC K100M were varied. In the first three formulations i.e F1, F2, F3 the concentration of HPMC K4M was used in proportion of 8, 23 and 38 respectively. In next three formulations i.e, F4, F5,F6 were prepared by changing polymer i.e., HPMC K15M which was used in proportion of 8,23 and 38 respectively and F7,F8,F9 were prepared by changing polymer i.e., HPMC K100M in proportion of 8,23 and 38 respectively. HPMC K4M, HPMC K15M, HPMC K100M and Xanthum gum were used as rate controlling agent for the release of drug and sodium bicarbonate as effervescent agent.*
Results: *The prepared tablets were evaluated for parameters like weight variation, hardness, friability, content uniformity, in-vitro buoyancy, floating lag time, swelling characteristics and in-vitro dissolution studies.*
Conclusion: *The tablets containing Metoclopramide hydrochloride, HPMC K4M and xanthum gum(F3) released 99.69% of drug by the end of 12th hour .*
Keywords: *Metoclopramide, Bilayered tablet, Floating, Effervescent , Controlled release.*

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I. Introduction

A bilayered tablet is made up of two separate layers which are formulated to separate physically or chemically incompatible ingredients or to produce repeat action or to dissolve at different times or to deliver the product at different locations or to give different pharmacological effects. The first layer is the floating layer which helps in floating of tablet and the second layer or the core tablet shall be retained in the stomach for a sustained release of drug. [1]

Bilayered tablet is used for controlling the delivery rate of eithersingleor two different active pharmaceutical ingredient/s (API) and to modify the total surface area available for API layer (drug) either by sandwiching with one or two inactive layers in order to achieve swell able/erodible barriers for modified release. [2]

Floating drug delivery system (FDDS) is designed to have a low density and thus float on gastric contents after administration until the system either disintegrates or absorbs. There are two types of FDDS. They are effervescent systems and non-effervescent systems.Effervescent systemsfloat in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas while the system is floating on the gastric contents , the drug is released slowly at the desired rate from the system. These are buoyant delivery systems, utilizing effervescence reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2,which gets entrapped in the jellified hydrocolloid layer of the system.Thus decreases its specific gravity and making it float over chime.[3]

A multiple unit type of floating pills, which generate CO_2, have also been developed. The system consists of a sustained release (SR) pill as seed, surrounded by double layers.[4] The inner layer is an effervescent layer containing sodium bicarbonate and tartaric acid. The outer layer is of a swellable membrane

layer containing PVA, shellac and others. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generated and entrapped carbon dioxide within the system.[5]

Another effervescent system consisting of a collapsible spring, which controls the release of drug from the polymer matrix which has also been developed. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating which is insoluble but permeable, allows permeation of water. Thus, carbon-dioxide is released, causing the beads to float in the stomach.

Single sided press

Various types of bi-layer presses have been designed over the years. The simplest design is a single sided press with both chambers of the double feeder separated from each other. Each chamber is gravity- fed or forced-fed with different powder, thus producing the two individual layers of the tablet. When the die passes under the feeder, it is at first loaded with the first-layer powder followed by the second-layer powder. Then the entire tablet is compressed in one or two steps (two = pre- and main compression). The two layers in the die mix slightly at their interface and in most cases bond sufficiently so that no layer-separation occurs when the tablet is produced. This is the simplest way of producing a bilayer tablet.[6, 7]

The aesthetic appeal this bi-layered floating tablet is expected to sustain the drug release, reducing the dose, reducing frequency of administration and improve its bioavailability thus improving the patient compliance. Metoclopramide Hydrochloride has biological half-life of nearly 5-6 hours. An attempt was made to sustain its release by using two different polymers.

. The relatively small daily dose, short half-life, undesirable side effects and rapid absorption from GIT make metoclopramide hydrochloride is a good candidate for formulation in a gastro retentive dosage form. Thus to reduce the dosage frequency and the dose of metoclopramide hydrochloride it can be formulated as floating tablets in gastrointestinal tract to sustain the drug release. The antiemetic action of metoclopramide is due to its antagonist activity at D_2 receptors in the chemoreceptor trigger zone (CTZ) in the central nervous system (CNS)—this action prevents nausea and vomiting triggered by most stimuli .[9]At higher doses, 5-HT_3 antagonist activity may also contribute to the antiemetic effect, gastroprokinetic effect, gastro esophageal reflux disease (GERD).

In the present study, formulations were done to develop bilayered floating tablets of Metoclopramide hydrochloride which give longer half-life, decreasing the frequency of dosing and thus decreasing the undesirable side effects.

II. Material And Methods:

Metoclopramide and the excipients Sodium bicarbonate, Magnesium stearate, Talcum powder , Hydrochloric acid is obtained from S.D.Fine chemicals,Mumbai. Hydroxy propoyl methyl cellulose(HPMC K4M),Hydroxy propoyl methyl cellulose(HPMC K15M) , Hydroxy propoyl methyl cellulose(HPMC K100M). Xanthum gum obtained from Essel fine chem, Mumbai.

Metoclopramide is white crystalline powder, very soluble in water, ethanol (95%); sparingly soluble in dichloromethane; practically insoluble in ether. It is having half-life (5±1 hour) and usually administered in a per-oral dose of 10-15mg four times daily as immediate release tablets.

Methodology:

Bilayer floating tablet (BFT):-

Metoclopramide with polymers of HPMC-K4M, HPMC-K15M, HPMC-K100M and xanthum gum were employed in the release layer formulation for the controlled delivery of the drug .[10]Floating layer contains xanthum gum and an effervescent agent sodium bicarbonate. Drug layer comprised of 100mg and floating layer of 150mg making into 250mg of Metoclopramide HCL tablet. To each layer, 1%magnesium stearate was added as lubricant before compressing with single tablet hand press of 8-mm flat plain punch diameter by direct compression technology. The prepared tablets were evaluated visually for their appearance, texture and tablets defects and then evaluated for weight variation[11], hardness, drug content[12], floating behaviour, and *in vitro* dissolution studies as per IP specifications and the reading were statistically analyzed by calculating mean and standard deviation of the finding of drug release.[13]*In vitro* buoyancy studies done by evaluation of swelling index, floating time, floating lag time.

The *in vitro* buoyancy was determined by floating lag time and total floating time. [14]

The tablets were placed in a 100 ml 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 (TFT).

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of the tablets was determined by placing the tablets in the basket of the dissolution apparatus using dissolution medium as 0.1N HCl at 37 ± 0.5°C. After 0.5, 1, 2, 3, 4, 5, and 6 hours, each dissolution basketcontaining tablet was withdrawn, blotted with tissue paper to remove the excess water and weighed on theanalytical balance. The experimentwas performed in triplicate for each time point. Swelling index was calculated by using the followingformula.[15]

$$\text{Swelling index\%} = \frac{\text{(Wet weight of tablet at time 't'- Dry weight of tablet)}}{\text{Dry weight of tablet}} \times 100$$

III. Results

Table 1:- Formula Composition of Metoclopramide Hydrochloride sustain release layer (100mg)

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	15	15	15	15	15	15	15	15	15
HPMC K4M	8	23	38	-	-	-	-	-	-
HPMC K15M	-	-	-	8	23	38	-	-	-
HPMC K100M	-	-	-	-	-	-	8	23	38
Xanthum gum	7	7	7	7	7	7	7	7	7
Microcrystalline cellulose	68	53	38	68	53	38	68	53	38
Magnesium stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1

Table 2: Composition of formulation of floating layer (150mg)

S.no.	Ingredients	Quantity(mg)
1	Xanthum gum	75
2	Sodium bicarbonate	30
3	Microcrystalline cellulose	42
4	Magnesium stearate	1.5
5	Talc	1.5

Table No. 5: Evaluation of parameters of Tablets

Formulation code	Weight variation	Hardness (kg/cm^2)	Friability (%)	Thickness(mm)	Content uniformity
F1	245 ± 0.6	5.3 ± 0.30	0.72 ± 0.12	4.35 ± 0.02	86.57 ± 0.21
F2	243 ± 0.8	5.5 ± 0.25	0.68 ± 0.09	4.36 ± 0.01	95.35 ± 0.17
F3	244 ± 0.2	5.5 ± 0.20	0.59 ± 0.08	4.35 ± 0.02	99.73 ± 0.14
F4	241 ± 0.7	5.4 ± 0.30	0.66 ± 0.15	4.33 ± 0.03	91.40 ± 0.20
F5	236 ± 0.6	5.8 ± 0.40	0.68 ± 0.06	4.34 ± 0.01	97.54 ± 0.13
F6	240 ± 0.3	5.6 ± 0.15	0.69 ± 0.04	4.35 ± 0.02	92.71 ± 0.12
F7	237 ± 0.1	5.3 ± 0.20	0.58 ± 0.13	4.35 ± 0.04	92.71 ± 0.35
F8	244 ± 0.9	5.6 ± 0.15	0.65 ± 0.16	4.36 ± 0.02	87.45 ± 0.12
F9	241 ± 0.7	5.5 ± 0.25	0.56 ± 0.15	4.35 ± 0.03	98.61 ± 0.15

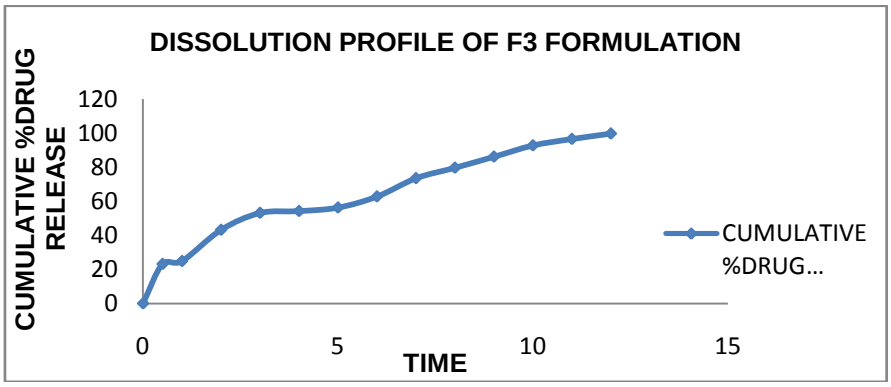
Table No. 6: Results of floating parameters of Tablets

Formulation code	Floating lag time (s)	Floating time (h)	Swelling index (%)
F1	88 ± 10.1	12	85.32
F2	54 ± 0.2	12	81.48
F3	25 ± 0.2	12	99.14
F4	54 ± 0.5	12	81.03
F5	80 ± 0.1	12	44.64
F6	44 ± 0.3	12	87.48
F7	33 ± 0.4	12	92.07
F8	60 ± 0.5	12	85.48
F9	62 ± 0.5	12	86.02

Table No.7:- Results of *In-vitro* drug release - time cummulative percentage drug release

Time(h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	24.22	54.85	23.11	56.27	69.85	30.53	19.32	19.48	29.90
1	99.22	66.06	24.85	77.90	82.32	50.74	63.06	86.43	41.27

2	-	77.58	43.16	93.22	87.53	60.06	82.48	88.32	52.64
3	-	84.69	53.11	97.48	87.85	87.06	87.37	92.74	71.58
4	-	89.27	54.22	-	93.85	89.74	89.58	93.06	78.22
5	-	92.90	56.27	-	96.22	91.32	89.90	93.85	79.01
6	-	94.01	62.74	-	97.16	94.80	91.80	94.32	87.06
7	-	97.01	73.48	-	99.85	96.22	95.11	95.43	88.80
8	-	99.06	79.64	-	-	97.32	98.43	97.32	91.64
9	-	99.69	86.11	-	-	98.90	-	99.53	93.37
10	-	-	92.74	-	-	99.69	-	-	98.43
11	-	-	96.53	-	-	-	-	-	-
12	-	-	99.69	-	-	-	-	-	-



Graph No. 1:- F3 formulation dissolution graph of time verses cumulative drug release.

KINETIC MODELS:

Table No.10: Stability study of F3

S.no	Parameters	Initial	1month	2month	3month	Limits as per specification
1	40^0c/75%RH %drug Release	99.69	99.23	99.02	98.32	Not less 85%
2	40^0c/75%RH %Release	99.73	99.62	99.43	99.18	Not less than 90% Not more than 110%

IV. Discussion

In the present study, an attempt has been made to formulate and evaluate bilayer floating tablets of Metoclopramide hydrochloride employing swellable polymers like Hydroxy propyl methylcellulose of various viscosity grades like HPMC K4M, HPMC K15M, HPMC K100M, Xanthum gum, inert excipients like talc, magnesium stearate. Nine formulations were prepared by altering the ratios of Polymers. The formulations were subjected to both pre and post formulation studies.

Tablet thickness, hardness, weight variation, friability and drug content of formulated Tablets of batches from F1 to F9 are presented in Table 5 of results.

The weight of all the tablets was found to be uniform with low values of 0.1 standard deviation and within the prescribed IP limits of ±7.5%.

The hardness of the tablet formulations was found to be in the range of 5.3-5.5 kg/cm2 .

The friability values were in the range of 0.56-0.72.

In vitro dissolution studies were performed on the all formulations from F1-F9 and results are shown in Table 5 .The drug content uniformity of F3 was found to be 99.73±0.14 which is the total amount of drug released up to 12hours where almost complete drug release was achieved.

Floating lag time was found to be in the range of 33-88 sec. The floating time and swelling index were 12hrs and 99.14% respectively for F3 formulation.

Drug release kinetics was done for all formulations. The line of equations and regression coefficient of kinetic study for F3 formulation was shown in table 8. The regression coefficient was considered as main parameter to interpret release kinetics. The optimized formulation F3 followed Higuchi model with R^2 value of 0.985 and zero order release as shown in table 9.

Stability study showed no significant change in physical and chemical properties of the tablets of formulation F3 after 3 Months, parameters like percentage drug release and assay values at various conditions(at 40^0C/ 75% RH) as per ICH guidelines quantified at various time intervals were shown in table 10.

V. Conclusion

Metoclopramide Hydrochloride floating tablets were prepared by direct compression method incorporating varying concentrations of HPMC K4M, HPMC K15M, HPMC K100M and Xanthan gum as rate controlling agents and sodium bicarbonate as effervescent agent. The prepared tablets were evaluated for different parameters like weight variation, hardness, friability, content uniformity, *In-vitro* buoyancy, floating lag time, swelling characteristics and *In-vitro* dissolution studies. The tablets containing Metoclopramide hydrochloride, HPMC K4 and xanthum gum released 99.69% of drug at the end of 12^{th} hour by the *in-vitro* drug release study.

Study concluded that promising sustain release gastro retentive floating bilayer tablets was developed by using combination of HPMC K4M and Xanthan gum. The floating bilayer tablets of Metoclopramide hydrochloride was capable of maintain plasma drug concentration through 12 hours.The release rate of drug from the floating bilayer tablets was significantly influenced by the proportion as well as viscosity of polymer used .The formulation F3 was selected as an optimized formulation because it gave the best results in *in-vitro* buoyancy study, good floating integrity, sustained release of drug and best fitted to Higuchi model with R^2 value of 0.985 and zero order release. Short –term stability studies indicated no appreciable changes in *in-vitro* drug release rates of formulation F3.

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