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Development of Metclopramide Floating Tablets Based on HPMC Matrices: A Comparison Study with Marketed Formulation

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Research Article

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Abstract

Objective: The objective of this study was to develop a floating matrix tablet of Metoclopramide based on HPMC matrices and check the effect of controlled release property of the drug with marketed formulation.

Method: Tablets are prepared by wet granulation method by using HPMC, Sodium starch glycolate and sodium bicarbonate as polymers and excipients. PVP K 30 (5% in IPA) used as granulating agent.

Results: Floating properties of the tablets were determined by determination of density, floating lag time, floating duration and in vitro drug release. Tablets of all the batches had desired buoyancy characteristics.

Conclusion: It was concluded that upon increase in concentration of sodium bicarbonate and sodium starch glycolate in the HPMC matrices sustained the drug release. From the comparison studies it was found that developed formulation were more effective due to patient compliance.

Keywords: *Floating tablets, Floating drug delivery systems (FDDS), HPMC Matrices, Metclopramide*

Introduction

Unpredictable gastric residence time (GRT) of a controlled release dosage form leads to interest in targeting and retaining the dosage form in the stomach for a prolonged period of time[1]. Thus Retention of drug delivery systems in the stomach prolongs overall gastrointestinal transit time and improves the oral bioavailability of the drugs that are having site-specific absorption from the stomach or upper part of the small intestine. Therefore different approaches have been proposed to retain the dosage form in the stomach including bioadhesive systems [2], swelling and expanding systems[3-4], floating systems[5-6] and delayed gastric emptying devices[7]. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the 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 fluctuations in plasma drug concentration [8].

Metoclopramide Hydrochloride (MCP) is used as a model drug for the present study, to produce Floating drug delivery system. MCP is 4-amino-5-chloro-N-[2-(diethyl amino) ethyl]-2 methoxy benzamide monohydrochloride monohydrate. It is one of the potent antiemetic drugs. MCP apparently antagonizes dopamine at the receptor sites. This action can explain its sedative, central antiemetic (blocks dopamine in the chemo-receptor trigger zone), extrapyrimidal, and prolactin secretion stimulation effects. It is used to treat the emesis caused due to chemotherapy in cancer patient. Due to Dopamine (D2) receptor blocking action the drug is showing extra-pyramidal (Parkinsonism like) symptoms, if administered in conventional dosage form but the patient's compatibility can be improved if administered in controlled release dosage form. Metoclopramide Hydrochloride is commonly used for the treatment of nausea and vomiting. This drug is highly water soluble and is rapidly absorbed after oral administration. It has a short biological half-life (5 ± 1 hour) and is usually administered in a dose of 10 to 15 mg four times daily in order to maintain effective concentrations throughout the day. In long term therapy, fluctuation in the plasma concentration, with high concentration peaks are common for drugs with rapid absorption and elimination. The secondary

effects of metoclopramide hydrochloride on the central nervous system in the form of extrapyramidal symptoms, if plasma levels markedly exceed therapeutic levels. Such characteristics make metoclopramide hydrochloride as best suitable drug candidates for controlled drug delivery [9-10-11].

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because they make it easier to achieve a desirable drug-release profile, they are cost effective, and they have broad US Food and Drug Administration acceptance [12]. The hydrophilic polymer matrix system consists of hydrophilic polymer, drug, and other excipients distributed throughout the matrix. This dynamic system is dependent on polymer wetting, hydration, and dissolution for controlled release of drug.

The objective of this study include (1) developing floating drug delivery system containing Metoclopramide and various polymers (HPMC K 4M, carbopol, Sodium starch glycolate, sodium bicarbonate and citric acid etc). (2) Study the effect of controlled release property of the drug with marketed formulation.

Material and Method

Materials

Metoclopramide was received as a gift sample from Cipla Ltd., India, hydroxypropyl methylcellulose (HPMC K4M), obtained as a gift sample from Colorcon Asia Pvt Ltd., Goa-India, sodium starch glycolate was obtained as a gift samples from Signet Chemicals, Mumbai, India, Sodium bicarbonate, PVP K30, citric acid magnesium stearate, talc and all other chemicals used were of analytical grade.

Methods

Fabrication of MCP Floating Tablets

Tablets were prepared by conventional wet granulation method according to table 1. The various polymers along with 20mg drug were thoroughly mixed and passed through sieve no. 40. Granulation was done with a solution PVP K30 (5%, w/v, in isopropyl alcohol). The wet mass was passed through sieve no. 20 and dried in a hot air oven at 40 °C for 6 h. The dried granules were lubricated with magnesium stearate and talc and compressed into a tablet on a Cadmach single station tablet press.

Table 1. Formulation and Composition of metoclopramide floating tablets

Formulation	FH1	FH2	FH3	FH4	FH5	FH6	FH7	FH8	FH9	FH10	FH11	FH12
Composition(mg/tablet)												
Metoclopramide	20	20	20	20	20	20	20	20	20	20	20	20
HPMC K4 M	100	150	200	250	200	250	250	150	250	200	200	250
Sodium bicarbonate	30	30	30	30	50	70	100	30	30	30	30	30
Sodium Starch Glycolate	20	20	20	20	-	20	20	20	20	50	100	50
Citric Acid	-	-	-	-	-	-	-	20	20	-	-	-

Evaluation of Formulation

Determination of Density

The tablet density of the floating system was determined by displacement method, using benzene as a displacing medium. A plethysmometer was employed to measure tablet density. Firstly, the instrument was calibrated using for its volumetric capacity (density 0.8723g/cc) for its volumetric capacity. Benzene was filled till a mark in capillary of the instrument. Subsequently, five tablets of known weight were dropped in wider mouth of the plethsmometer. The system was kept undisturbed for 1 min, to let benzene displace the air in the pores of the tablets. After that, displacement in the volume of the benzene in the side capillary was noted. Knowing the weight and volume occupied by the tablets, density of five tablets was determined [13].

Floating Properties

The time taken for tablet to emerge on surface of medium is called the floating lag time (FLT) and duration of time the dosage form to constantly remain on surface of medium is called the total floating time (TFT). The buoyancy of the tablets was studied in USP 24 type II dissolution apparatus at 37±0.5°C in 900 ml of 0.1N HCl at pH 1.2. The measurements were carried out for each formulation of tablets (n=6). The time of duration of floatation was observed visually [14].

Swelling Index

Metoclopramide tablets were weighed individually (W_0) and placed in 900ml of dissolution medium (0.1 N HCl). The temperature was maintained at 37 ^{0}C. At regular intervals, the samples were removed using a small basket and swollen weight (W_t) of each tablet was determined at predefined time intervals [15]. The percentage swelling index was calculated by equation1.

Percentage swelling index = W_t-W_0/ W_0 x W_0.....Eqn.1

Where W_0 is the initial weight of tablet, and W_t is the weight of tablet at time t.

Assay of Tablet

Six tablets from each batch were weighed and powdered. Powder equivalent to the average weight of the tablet was accurately weighed and transferred into a 100-mL volumetric flask and dissolved in a suitable quantity of distilled water. The solution was made up to the mark and mixed well. A portion of the sample was filtered and analysed by a UV spectrophotometer (Double-beam Lab India 3000+) at 293 nm.

Physical Characterization

The fabricated tablets were characterized for weight variation (n = 20), hardness (n = 10) (Monsanto hardness tester), and thickness using a screw-gauge micrometer (Mityato, Japan).

***In vitro* Release study**

The release of metoclopramide was studied using USP dissolution apparatus II. The dissolution medium was 0.1N HCl 900 ml, (37±0.5^0 C) at 100 rpm. Five milliliters of aliquot was withdrawn at predetermined time intervals of 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 24 h and volume replaced with equivalent amount of dissolution medium. The samples were analyzed by using UV Spectroscopy at 273 nm.

Comparative dissolution study with marketed Formulation

A comparison study of optimized formulation with marketed formulation (Perinorm) was done using USP dissolution apparatus II. The dissolution medium was 0.1N HCl 900 ml, (37±0.5^0 C) at 100 rpm. Five milliliters of aliquot was withdrawn at predetermined time intervals of 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 24 h and volume replaced with equivalent amount of dissolution medium. The samples were analyzed by using UV Spectroscopy at 273 nm.

Results & Discussion

Determination of tablet density

Apparent tablet density of all the formulation was found to be in the range of 0.751±0.090 to 0.895±0.029. Density of all the formulation was lower than the 1.008g/cm^3. The density of the formulation decreases with the increase amount of HPMC, sodium starch glycolate and sodium bicarbonate concentration. The variation of tablet density was due to difference in porosity nature of the polymers used in the formulation the polymers having the less porous nature were found to be having more tablet density.

Floating Properties

All the batches of tablets were found to exhibits the short floating lag times due to presence of sodium bicarbonate.

After an initial floating lag time all the floating tablets were floating till the matrix remained due to the sodium bicarbonate. Sodium bicarbonate induces CO_2 genration in the presence of acidic media (0.1N HCl). The CO_2 generated was trapped and protected with in the gel formed by hydration of HPMC, carbopol and sodium starch glycolate matrices. Thus the specific gravity of tablets was become less than gastric fluids and the tablet become buoyant in gastric fluids for a long time.

All the formulation containing HPMC matrices with 20 mg metoclopramide float more than 12 hr. because HPMC hydrate only at the surface keep their original air bubbles for a longer period of time. The addition of sodium bicarbonate forces the floating behavior [16].

Swelling Index

The swelling of the polymers used (HPMC K4M and sodium starch glycolate) could be determined by water uptake of the tablet. The percent swelling of the tablet was determined by the method described above at different time intervals. The complete swelling was achieved by the end of 8 h, so percent swelling was determined at the end of 8 h for all the developed formulations. (Table 2)

Assay of Tablet

The drug content in all the batches of metoclopramide floating tablet was in the range of 98.17 to 101.1% (i.e., a variation of ±5%). This ensured the uniformity of the drug content in the tablets.

Physical Characterization

Weight variation data of the prepared tablets indicated no significant difference in the weight of individual tablets from the average value. Hardness of prepared tablets was observed within the range of 3.1±0.134 to 4.1±0.109. Friability of all the tablets was below 1%., which is indicated that good mechanical resistance of the tablets.

***In vitro* Release study**

Ideally, an extended-release tablet should release the required quantity of drug with predetermined kinetics in order to maintain an effective drug plasma concentration. To achieve this, the tablet should be formulated so that it releases the drug in a predetermined and reproducible manner. By considering the drug's biopharmaceutic and pharmacokinetic profile, one can determine the required release from the tablet [17].

Fig. 1 shows the release of all the formulation from prepared batches from the release studies it was found to be all the formulation sustained the drug release up to 12 hours minimum due to HPMC matrices. Formulation FH1, FH2, FH3 and FH4 shows almost 100% drug release at the end of 12th hour and maintained the integrity of formulation throughout the dissolution. It is due to the hydrophilic properties of HPMC and gelling property of these matrices. Formulations FH8 and FH9 shows the cumulative amount of release up to 12th hour but the initial drug release was found to be burst drug release and formulation does not maintained the physical integrity it may be due to the addition of sodium bicarbonate. Formulation FH10, FH11 and FH12 does not maintained the physical integrity for the entire duration of dissolution due to the more amount of sodium starch glycolate which is super disintegrant and absorb the water twice to its weight.

Formulation FH6 and FH7 shows the good release profile up to 20 hours and their swelling characteristics are also good but the formulation FH6 was found to be best due to swelling character, release properties and physical integrity.

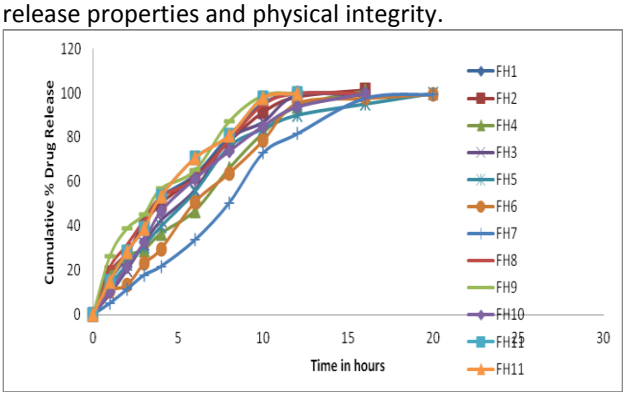

Fig. 1 Cumulative Percentage drug release from all the batches of prepared tablets.

Table 2. Percentage swelling of formulation with Time

Time	Percentage Swelling											
(hr)	FH1	FH2	FH3	FH4	FH5	FH6	FH7	FH8	FH9	FH10	FH11	FH12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	20.48	28.98	39.44	42.31	39.53	40.23	36.23	44.44	46.98	41.35	51.76	62.48
2	42.65	44.87	53.98	53.48	51.98	58.76	53.03	53.35	56.08	53.76	71.31	85.79
3	57.89	59.43	66.18	67.26	65.14	65.26	80.67	68.81	70.32	67.51	79.34	109.10
4	73.44	90.83	98.01	130.91	99.97	105.19	120.89	109.01	128.40	110.09	140.97	136.13
5	101.34	96.53	150.91	151.06	149.63	158.12	154.09	150.05	190.82	145.93	171.89	160.68
6	133.72	135.27	199.77	199.11	189.72	197.48	195.72	190.35	228.87	194.23	199.32	197.93
7	159.68	174.72	198.31	203.37	198.89	201.98	204.12	199.89	195.41	204.65	220.97	212.68
8	178.55	199.48	219.89	222.76	223.32	228.44	230.04	218.02	170.23	232.87	259.34	229.17
10	150.78	160.12	199.31	199.04	199.78	196.31	198.78	190.48	140.98	202.76	195.17	199.53
12	142.12	150.19	165.26	169.76	175.23	185.53	188.31	165.98	95.53	187.01	135.48	180.32

Analysis of release data

The dissolution data obtained were plotted as cumulative percentage drug released vs. time as zero order, Log cumulative percentage drug retained vs. time as First order release kinetics, Cumulative percentage drug released vs. square root of time as Higuchi equation and Log of fraction of drug released vs. Long time as per Korsmeyer and Peppas equation[18].

The drug release data were explored for the type of release mechanism followed. The best fit with the highest determination R^2 coefficients was shown by both the Higuchi and first order models followed by zero order which indicate the drug release via diffusion mechanism.

Table 3. Kinetics of in Vitro Release from Floating Tablets of Metoclopramide

Formulation	ZERO ORDER	FIRST ORDER	HIGUCHI	KORESMAYER	
Code	R^2	R^2	R^2	N	R^2
FH6	0.9068	0.9168	0.9377	0.8655	0.9657
FH7	0.9532	0.8549	0.9228	1.0408	0.9877

The value of n with regression coefficient for FH6 and FH7cformulations is shown in Table 3. The values of n were in the range of 0.52 to 1.0, indicating Non fickian release governed by the drug diffusion. However as indicated by the values of R^2 both of the models (Higuchi and Peppas) were found to be efficient in describing the release of Metoclopramide from the floating tablets.

Comparative dissolution study with marketed Formulation

Comparative dissolution study of Optimized formulation FH6 with marketed Formulation (Perinorm) was shown in Fig 2. From the dissolution it was found to be optimized formulation was sustained properties and showed more patient compliance then marketed formulation.

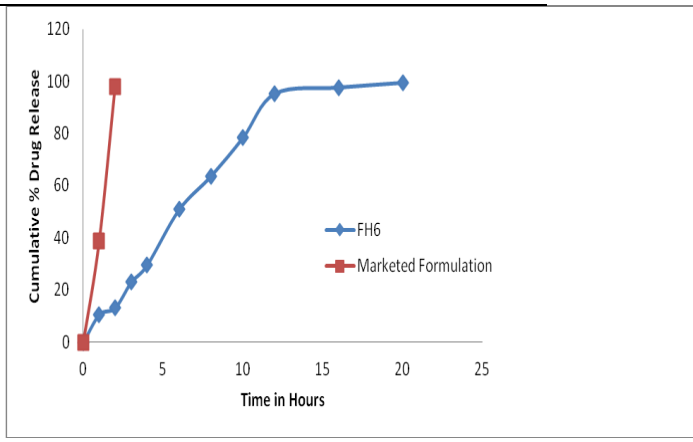

Fig. 2 Comparative dissolution study with marketed Formulation

Conclusion

We concluded that HPMC in combination with sodium starch glycolate and sodium bicarbonate cellulose can be promising polymers for effervescent gastroretentive drug delivery system of metoclopramide. Swelling studies indicate significant water uptake and contributed to drug release and could be significant in gastric retention. The formulations followed Higuchi kinetics while the drug release was found to be non fickian diffusion controlled. The developed floating tablets of metoclopramide may be used for prolonged drug release, as compared with marketed formulation, thereby improving the bioavailability and patient compliance.

References

1. Ali J, Arora S, Ahuja A, Babbar AK, Sharma RK, Khar RK. Formulation and Development of Floating Capsules of Celecoxib: In Vitro and In Vivo Evaluation. AAPS Pharm Sci Tech 2007; 8 (4):119.
2. Santus G, Lazzarini G, Bottoni G, et al. An in vitro-in vivo investigation of oral bioadhesive controlled release furosemide formulations. Eur J Pharm Biopharm. 1997; 44: 39-52.

3. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled-release drug delivery systems for prolonged gastric residence: an overview. Drug Dev Ind Pharm. 1996; 22: 531-539.
4. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled-release system for gastric retention. Pharm Res. 1997; 14: 815-819.
5. Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. J Pharm Sci. 1994; 83: 239-245.
6. Whitehead L, Fell JT, Collett JH, Sharma HL, Smith AM. Floating dosage forms: an in vivo study demonstrating prolonged gastric retention. J Control Release. 1998; 55: 3-12.
7. Chawla G, Bansal A. A means to address regional variability in intestinal drug absorption. Pharm Technol. 2003; 27: 50-68.
8. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release 2000; 63: 235-259.
9. Yadav D R, Ayyappan T, Shanmugam S, Sundaramoorthy K, Vetrichelvan T. Development and in-vitro evaluation of buccoadhesive metoclopramide hydrochloride tablet formulations. Int J PharmTech Research 2011; 3(1): 516-25.
10. Sayed AR, Gamal MM, Badry M. Preparation and comparative evaluation of sustained release metoclopramide hydrochloride matrix tablets. Saudi Pharm J 2009; 17:283-8.
11. Patel M, Kumar AP, Kulkarni S, Rao S. Design And Evaluation Of Controlled Release Matrix Tablets Of Metoclopramide Hydrochloride Using Hydrophilic Polymers. Int J Curr Pharma Res.2012; 4 (3):64-69
12. Alderman DA. A review of cellulose ethers in hydrophillic matrices for oral controlled-release dosage forms. Int J Pharm Tech Prod Mfr. 1984; 5: 1-9.
13. Sangekar S, Vadino WA, Chaudry I, Parr A, Beihn R, Digenis G, Evaluation of the effect of food and specific gravity of tablets on gastric retention time. Int J Pharm. 1987; 35: 187–191.
14. Kiran MK, Shah MH, Ketkar A, Mahadik KR, Paradkar A. Effect of drug solubility and different excipients on floating behavior and release from glyceryl monooleate matrices. Int J Pharm 2004; 272: 151-160.
15. Srivastava AK, Wadhwa S, Ridhurkar D et al. Oral Sustained Delivery of Atenolol from Floating Matrix Tablets - Formulation and In Vitro Evaluation. Drug Dev Ind Pharm. 2005; 31: 367-374.
16. Sanchez PEG, Leon AH, Robles LV. Effect of Sodium Bicarbonate on the Properties of Metronidazole Floating Matrix Tablets. Drug Dev Ind Pharm. 2008; 34:171–180.
17. Merchant HA, Shoaib HM, Tazeen J, & Yoysuf RI. Once-daily tablet formulation and in vitro release Evaluation of Cefpodoxime Using Hydroxypropyl Methylcellulose: A Technical Note. AAPS Pharm Sci Tech. 2006; 7(3): 78.
18. Garg R, Gupta GD. Preparation and Evaluation of Gastroretentive Floating Tablets of Silymarin. Chem Pharm Bull 2009; 57(6): 545—549.

AUTHORS' CONTRIBUTIONS

Authors contributed equally to all aspects of the study.

PEER REVIEW

Not commissioned; externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.