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THE INFLUENCE OF pH ON DRUG RELEASE FROM METFORMIN HCL MATRICES CONTAINING DIFFERENT GRADES OF HYDROXYPROPYL METHYL CELLULOSE

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ABSTRACT

The present study examines the effect of multimedia dissolution profile on the drug release of sustained release hydrophilic matrices of metformin hydrochloride containing combination of different grades of hydroxypropyl methylcellulose. Metformin HCL, the only available biguanide, remains the first line drug therapy for patients with Type 2 diabetes mellitus acts by decreasing hepatic glucose output and peripheral insulin resistance. It has relatively short plasma half-life and low absolute bioavailability. Hydrophilic matrices were prepared using combination of different grades of HPMC viz. HPMCK4M and HPMCK15M to sustain the release of the drug. Multimedia dissolution studies were performed to mimic the in-vivo condition by doing in-vitro test. The pH/buffer selection is based on the exposure of drug from stomach to intestine/colon. The study ensures the impact of pH changes on dissolution and release of drug substance for absorption. Hydrophilic matrices of metformin hydrochloride also provide quite regulated release of the drug over an extended period of time.

Key words: Multimedia Dissolution, Hydrophilic matrices, HPMC, pH.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a worldwide public health challenge. The morbidity, mortality and economic consequences of T2DM are still a great burden to patients, society, health care systems and the economy. The existing treatments for glycaemic control have limitations either because of their side effects (particularly weight gain and hypoglycaemia) or contraindications that limit their use. Metformin HCL, the only available biguanide, remains the first line drug therapy for patients with T2DM, acts by decreasing hepatic glucose output and peripheral insulin resistance. The advantages of metformin are a very low risk of hypoglycaemia, weight neutrality and reduced risk of cardiovascular morbidity and mortality. It is an oral anti-hyperglycemic agent, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50% – 60 % with relatively short plasma half-life of 1.5 - 4.5 h. An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhoea that especially occur during the initial weeks of treatment. Side effects and the need for administration two or three times per day when larger doses are required can decrease patient compliance. A sustained-release formulation that would maintain plasma levels of the drug for 10 to 12 hours might be sufficient for once-daily dosing of metformin [1-6].

Sustained release drug delivery system of metformin hydrochloride is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time by using different grades of hydroxypropyl methylcellulose (HPMC) viz. HPMCK4M and HPMCK15M [7-11].

Multimedia dissolution is to mimic the in-vivo condition by doing in-vitro test and pH/buffer selection is based on the exposure of drug from stomach to intestine/colon and to ensure the impact of pH changes on dissolution and release of drug substance for absorption [12-14].

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MATERIALS AND METHODS

Metformin hydrochloride was obtained as a gift sample and HPMCK4M and HPMCK15M were obtained from Colorcon India Ltd., Goa. Magnesium stearate, Talc, MCC, dibasic calcium phosphate and other reagents used were of analytical grade.

Tablets were prepared by direct compression using HPMCK4M and HPMCK15M polymer combinations. The drug was analyzed by UV spectrophotometer (UV 1601 Shimadzu, Japan) at 233nm.

Physical Characterization

The tablets were subjected to their physical characterization. Hardness, friability and weight variation and found within the probable limits, Table [1].

Dissolution Studies

In order to study the effect of the dissolution medium pH on the drug release pattern, drug release was studied in phosphate buffer of pH 2.4, 6.8 and 7.4. The dissolution mediums of different pH were prepared for the studies. The drug was analyzed by UV spectrophotometer (UV 1601 Shimadzu, Japan) at 233nm.

EXPERIMENTAL

Three tablets of metformin hydrochloride were taken into three different pH of phosphate buffer (pH2.4, pH 6.8 and pH 7.4).The USP dissolution apparatus was set at rotation 50 rpm and temperature of the assembly was set at 37^0 C. The tablets were placed in above prepared three different media of different pH. Absorbance was measured at 233 nm by collecting sample at different time interval as follows 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hrs. Five milliliters aliquots were withdrawn at predefined intervals, and the volume of the dissolution medium was maintained by adding the same volume of dissolution medium. The percentage drug release was calculated at different time intervals at different pH. The graph was plotted between percent drug release and time for different dissolution media.

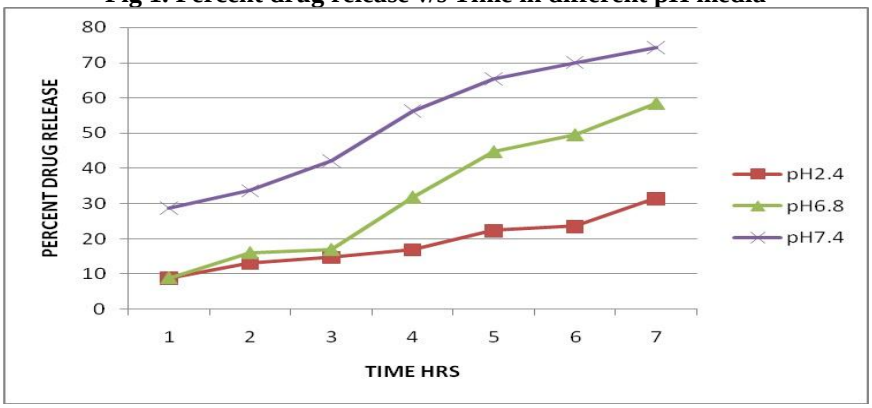
Table 1. Physical characteristics of the tablets

Formulation		Weight mg Mean ± SD	Hardness Kg Mean ± SD	Friability (%)
HPMCK4Mmg	HPMCK15Mmg			
90	80	750 ± 3.50	6.5 ± 0.12	0.50-0.70

Table 2. Result of dissolution studies with different pH

Sr. No.	Time hrs.	Absorbance (nm.)			% Drug release		
		pH 2.4	pH 6.8	pH 7.4	pH 2.4	pH 6.8	pH 7.4
1.	0.5	0.069	0.089	0.298	8.86	8.96	28.65
2.	1	0.120	0.143	0.279	13.10	16.06	33.58
3.	2	0.133	0.152	0.344	14.76	16.99	42.13
4.	3	0.150	0.266	0.527	16.96	31.90	56.28
5.	4	0.192	0.368	0.628	22.36	44.8	65.42
6.	6	0.194	0.402	0.639	23.53	49.6	70.10
7.	8	0.290	0.472	0.67	31.51	58.56	74.32
8.	10	0.365	0.629	0.753	44.76	80.1	83.62
9.	12	0.459	0.665	0.763	56.28	83.46	94.23

Fig 1. Percent drug release v/s Time in different pH media



RESULTS AND DISCUSSION

Physical properties of the tablets were found within the probable limits as shown in Table (1). The drug content was estimated from the absorbance obtained.Three tablets of metformin hydrochloride were placed into three different pH of phosphate buffer (pH2.4, pH 6.8 and pH 7.4).The USP dissolution apparatus was set at rotation 50 rpm and temperature of the assembly was set at 37^0 C. Absorbance was measured at 233 nm by collecting sample at different time intervals up to 12hrs. The percentage drug release was calculated at different time intervals at different pH and shown in Table (2). The graph was plotted between percent drug release and time for different dissolution media and shown in Fig (1).

CONCLUSION

The release profile of metformin hydrochloride from the matrices increased continuously with time, and the amount of drug release best seen in acidic media (pH=7.4). The cumulative amount of drug release is higher at pH 7.4 than that of pH 6.8 by 10.77 % and then that of pH 2.4 by 39.95 %. This increase in drug release at higher pH can be attributed to pH dependent solubility of metformin hydrochloride. As the pH increases, the solubility of metformin increases which might increase drug release from matrices.

REFERENCES

1. Ken F, Miranda P, Steven J. Glycemic control in patients with type 2 diabetes mellitus switched from twice-daily immediate-release metformin to a once-daily extended-release formulation. *Clinical Therapeutics*, 25(2), 2003, 515–529.
2. Mandal U, Gowda V, Ghosh A, Selvan S, Solomon S, Pal TK. Formulation and optimization of sustained release matrix tablet of metformin HCl 500 mg using response surface methodology. *Yakugaku Zasshi*, 127(8), 2007, 1281-90
3. Wadher KJ, Kakde RB, Umekar MJ. Formulation and evaluation of a sustained-release tablet of metformin hydrochloride using hydrophilic synthetic and hydrophobic natural polymer. *Indian J Pharm Sci*, 73(2), 2011, 208-15
4. Wadher JK, Kakde RB, Umekar MJ. Formulation of sustained release metformin hydrochloride matrix tablets: influence of hydrophilic polymers on the release rate and *invitro* evaluation. *International Journal of Research in Controlled Release*, 1(1), 2011, 9-16.
5. Goodman and Gilman's: The Pharmacological basis of therapeutics. 10th edition. Mc-Graw Hill, 2001, 709-710.
6. Ansel HC, Aallen LV, Popovich NG. Pharmaceutical dosage forms and drug delivery system, Lippincott Williams & Wilkins, Philadelphia (USA), 2002, 234-235.
7. Liam C, Feely and Stanley S. Davis. The influence of polymeric excipients on drug release from hydroxypropyl methylcellulose matrices. *International Journal of Pharmaceutics*, 44, 1988, 131-139.
8. Khan MA and Chaturvedi SC. Swelling and Drug Release Studies from Hydrophilic Matrices Containing Combination of Different Grades of Hydroxyl Propyl Methylcellulose. *Asian Journal of Chemistry*, 23, 2011, 3566-3568.
9. Khan MA, Studies of swelling effect and drug release in hydrophilic matrices containing different grades of polymers. *Research J. of Pharm. Biological and Chemical Sci*, (4)1, 2013, 1241-1247.
10. Khan MA, Maheshwari RK, Studies of relationship between swelling and drug release in the sustained release hydrophilic matrices containing different grades of hydroxyl propyl methylcellulose. *Research J. of Pharm. Biological and Chemical Sci*, 2(4), 2011, 970-975.
11. Swarbric J and Boylan JC. Encyclopedia of Pharmaceutical Technology, Marcell Dekker, New York, 1995.
12. Khan MA. Studies on diltiazem hydrochloride sustained release matrices profiles in multimedia dissolution conditions. *Research Journal of Pharmaceutical, Biological and Chemical Sciences (RJPBCS)*, 4, 2013.
13. Khan MA and Mehta RK. Studies on Multimedia dissolution Profile of Zolpidem Tartrate Sustained Release Matrix Tablets. *Research Journal of Pharmaceutical Biological and Chemical Sciences*, 3(2), 2012.
14. Khan MA. Studies on the effect of pH over dissolution profile of diclofenac sodium sustained release tablets. *Journal of Drug Delivery and Therapeutics*, 2(5), 2012, 65-66.