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DEVELOPMENT OF pH-INDEPENDENT CONTROLLED RELEASE MATRIX TABLETS OF PROPRANOLOL HCL

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ABSTRACT

In the present study, a pH-independent controlled release matrix system for acidic drugs was designed by incorporating release-modifiers in the formulation. Controlled release matrix tablets were prepared by compression of Propranolol hydrochloride. This study was to overcome pH -dependent release of weakly basic drug and to achieve pH independent drug release. An anti -hypertensive drug, Propranolol hydrochloride was chosen due to its pH -dependent solubility. One of the approaches to solve the problem of pH -dependent release of weakly basic drug has been done in this work. The water soluble and highly swellable HPMC was used as a matrix former and organic acids maleic acid, Succinic acid and fumaric acid were added to the drug polymer system in different formulations in varying proportions (at 10, 20, 40 and 80mg) as release modifiers. The addition of organic acids was found to maintain an acidic micro environmental pH inside the polymer matrices during drug release in phosphate buffer pH 7.4. On the other hand, the amount of each organic acid added to the system had no effect on the drug release in acidic solution 0.1N HCl. So the micro Environmental conditions for the dissolution and diffusion of drug were almost kept constant. Thus, the release of Propranolol hydrochloride from tablets containing HPMC and organic acids was found to be pH -Independent. Between the two organic acids, Succinic acid showed slightly better release when compared to Citric acid.

KEYWORDS: pH-independent, Propranolol hydrochloride, HPMC, controlled release systems.

INTRODUCTION

Most of the drugs are either weak acids or bases; their release from sustain release formulations is pH dependent in the GI fluid. During the course of GIT, drug may be exposed to various pH conditions ranging from acidity of stomach, weakly acidic duodenum to the alkaline environment of the small intestine. pH of the gastric environment affects the performance of orally administered drug. The pH of the stomach in fasted condition is about 1.5 to 2 & in fed condition, usually it is 2 to 6. A large volume of water administered with an oral dosage form changes the pH of stomach to the pH of the water initially. These changes occur because the stomach does not have enough time to produce a sufficient quantity of acid before emptying of liquid from the stomach.

Due to variable pH values observed in the GIT, the conventional controlled release matrices of ionizable drugs with pH - dependent solubility may give rise to intra and inter -individual variability's in bioavailability and this system is useful for increasing bioavailability of drugs. Therefore, pH-independent drug release system is desirable to assure a reliable drug therapy. The main objective of this research work to develop novel pH- independent SR matrix system for basic drugs was designed by incorporating release modifiers in the formulation. The main aim of this work is to overcome problems like variation in the absorption or reduction of bioavailability of drugs and intra and inter individual variability in bioavailability[1,2,3] In matrix system, the drug is dispersed homogeneously in a matrix of rigid non swellable hydrophobic materials or swells able hydrophilic materials.[4]The swellable hydrophilic materials are widely used for sustaining the release of highly water-soluble drugs. The materials for such metrics are generally hydrophilic gums like guar gum, karaya gum, and tragacanth etc. semi synthetic polymers like HPMC, CMC, and PEO etc.

MATERIALS AND METHODS

Materials

Drug (Propranolol Hydrochloride), were obtained as a gift sample from Sun pharmaceuticals India. HPMC were obtained as a gift sample from Micro Labs, Bangalore, India. All other chemicals used were of analytical grade.

Drug-excipient compatibility study

Thin layer chromatography was carried out to check for the possible drug- excipient interaction. The R_f values of the drug and excipients used in the study revealed negligible difference. This established that the drug and all the excipients used in the study revealed no interaction between them and indicated that they were compatible with each other.

Formulation of Propranolol HCl Matrix tablets

Propranolol HCl, polymer, organic acids (maleic acid ,succinic acid and fumaric acid) and diluents (Lactose DC) were first passed through sieve number 80 and accurate quantity was weighed mixed in geometric proportion using the mortar and pestle followed by lubrication using magnesium stearate (0.5 %). The physical mixture so obtained was subjected to compression using a 10- station 'Remix' mini press tablet punching machine using 8mm diameter flat punches. Organic acids including Maleic acid, succinic acid and fumaric acids with the concentrations of 5, 10 or 15% were introduced separately in the matrix formulations.The polymer used was HPMC K M. The hardness for the tablets was maintained at 54 kg / cm^2 in order to compare their In vitro release studies.[5,6]

IN VITRO RELEASE PROFILE

In vitro release study for all the formulations was carried out in dissolution test apparatus conforming to USP type II (Paddle Type). The water bath was thermo stated at 37^0 C ± 0.5^oC. The paddle was set to rotate at 50 rpm. One tablet, previously weighed, was kept in the dissolution media. Two dissolution Medias, acidic buffer pH 1.2 for twelve hours and Phosphate buffer pH 7.4 for twelve hours were used. 5ml of the dissolution medium was pipetted out at each hour into a 50ml volumetric flask and the volume was made up to the mark with the respective dissolution medium and analyzed by using an UV spectrophotometer against reagent blank. Each time 5ml of the respective fresh dissolution medium was replaced into the Jar.[7]

STABILITY STUDIES

Stability of a dosage form has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification.[8]

RESULT AND DISCUSSION

COMPATIBILITY STUDY

Compatibility study was carried out to check for any possible interaction between the drug and the excipients, for eight weeks at 50^0C. Thin layer chromatography was carried out and the R_f values were compared with that of R_f value for PPL HCl-IP at the end of the eight-weeks

Table 1: Drug- Excipient compatibility testing by TLC.

Spot. no.	Sample	R_f value
A	Propranolol Hcl	0.666
B	Propranolol Hcl +Lactose DC	0.652
C	Propranolol Hcl +HPMC4KM	0.680
D	Propranolol Hcl+ Maleic acid	0.675
E	Propranolol Hcl+ Succinic acid	0.681
F	Propranolol Hcl+ Fumaric acid	0.685

From the above results, it is observed that the difference between in R_f values between standard and the tests (drug: excipient mixtures) are negligible. Hence it can be inferred that the drug and excipient mixtures did not show any interaction during compatibility study.

Table 2: The composition of tablets prepared with or without organic acids.

Formulation* Code.	Propranolol Hcl	HPMC4000CPS	Lactose DC (%)	Magnesium sterate	Maleic acid (%)	Succinic acid (%)	Fumaric acid (%)
F0	38.0	30	37	1.5	-	-	-
F1	38.0	30	32	1.5	-	-	-
F2	38.0	27.5	34.5	1.5	-	-	-
F3	38.0	30	27	1.5	-	-	-
F4	38.0	25	32	1.5	-	-	-
F5	38.0	30	22	1.5	-	-	-
F_{MA10}	38.0	22.5	29.5	1.5	10	-	-
F_{MA20}	38.0	30	32	1.5	20	-	-
F_{MA40}	38.0	27.5	34.5	1.5	40	-	-
F_{MA80}	38.0	30	27	1.5	80	-	-
F_{SA10}	38.0	25	32	1.5	-	10	-
F_{SA20}	38.0	30	22	1.5	-	20	-
F_{SA40}	38.0	22.5	29.5	1.5	-	40	-
F_{SA80}	38.0	30	32	1.5	-	80	-
F_{FA10}	38.0	27.5	34.5	1.5	-	-	10
F_{FA20}	38.0	30	27	1.5	-	-	20
F_{FA40}	38.0	25	32	1.5	-	-	40
F_{FA80}	38.0	30	22	1.5	-	-	80

EFFECT OF pH OF DISSOLUTION MEDIA

There was remarkable difference in the release of propranolol HCl from HPMC-based matrices containing no organic acid (F0) in dissolution medias, namely, in simulated gastric fluid of pH 1.2 for twelve hours and in simulated intestinal fluid of pH 7.4 for twelve hours. Formulation F1 revealed a CDR of 25.02% at the end of 5hrs. in pH 1.2, where F5 resulted with a CDR of 15.34% at the end of 5hrs in pH-7.4. Formulation F5 revealed a CDR of 53.41% in pH 1.2 and 27.71% in pH 7.4 at the end of 12hrs. The possible reason for % CDR values has seen above is because of polymer HPMC. Swelling in contact with the dissolution media and the release of the drug from the matrix becomes diffusion controlled; the drug diffusing out through the water filled pores along a decreased drug concentration gradient (pH dependent solubility).

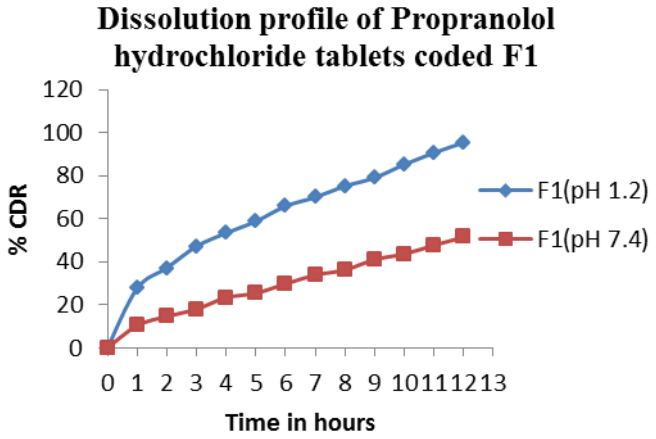

Fig.1: In vitro release rate profile of PPL HCl in Simulated gastric fluid (pH 1.2), Simulated Intestinal fluid (pH 7.4) Drug: polym1er ratio 1:1 F1.

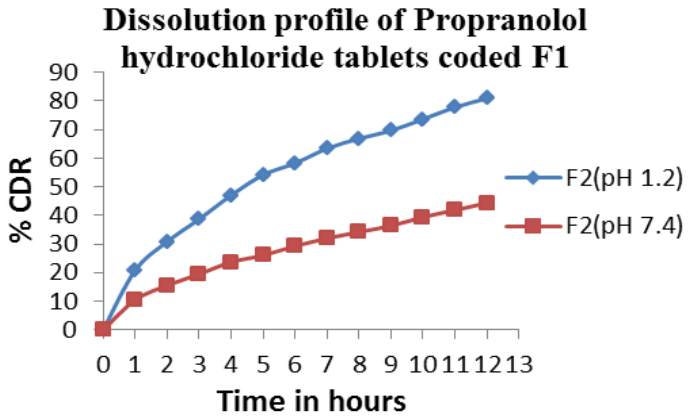

Fig.2: In vitro release rate profile of PPL HCl in Simulated gastric fluid (pH 1.2), Simulated Intestinal fluid (pH 7.4) Drug: polymer ratio 1:1.2 F2, 1:1.5F2.

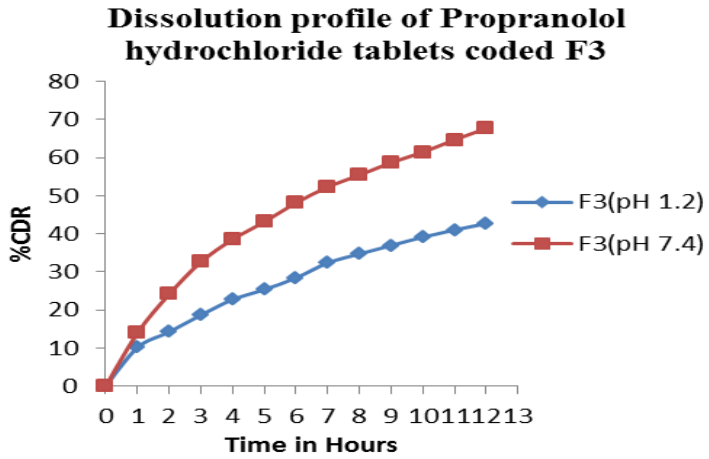

Fig.3 In vitro release rate profile of PPL HCl in Simulated Intestinal fluid (pH 7.4) Simulated gastric fluid(pH 1.2) Drug: polymer ratio 1:2 F3 ,1:2 F3.

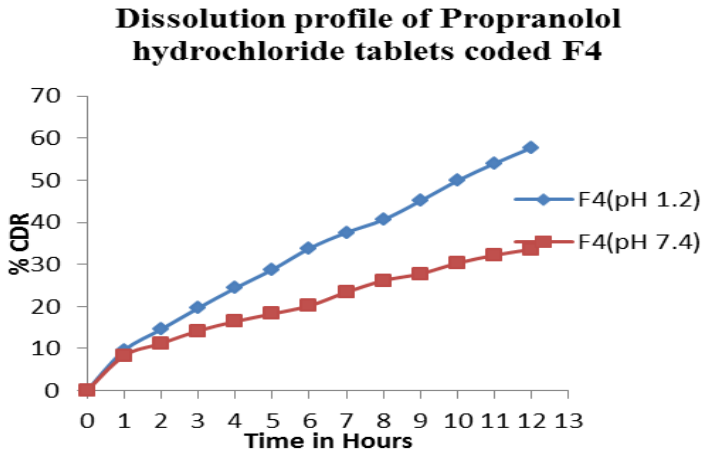

Fig.4: In vitro release rate p rofile of PPL HCl in Simulated gastric fluid(pH 1.2) , Simulated Intestinal fluid (pH 7.4)Drug: polymer ratio 1:2.5 F4, 1:2.5 F4.

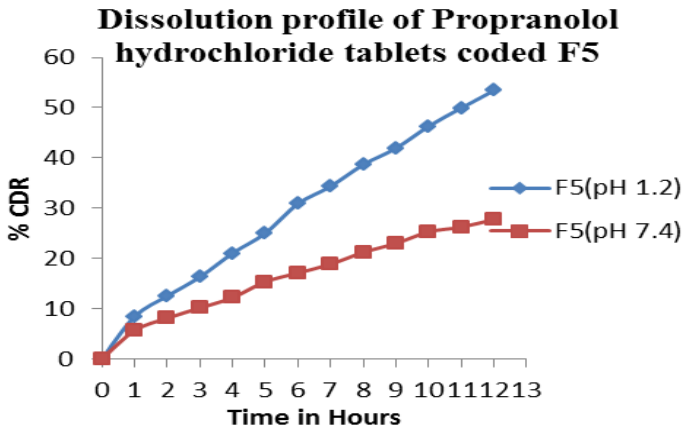

Fig.5: In vitro release rate profile of PPL HCl in Simulated gastric fluid (pH 1.2), Simulated Intestinal fluid (pH 7.4) Drug: polymer ratio 1:3 F5, 1:3 F5

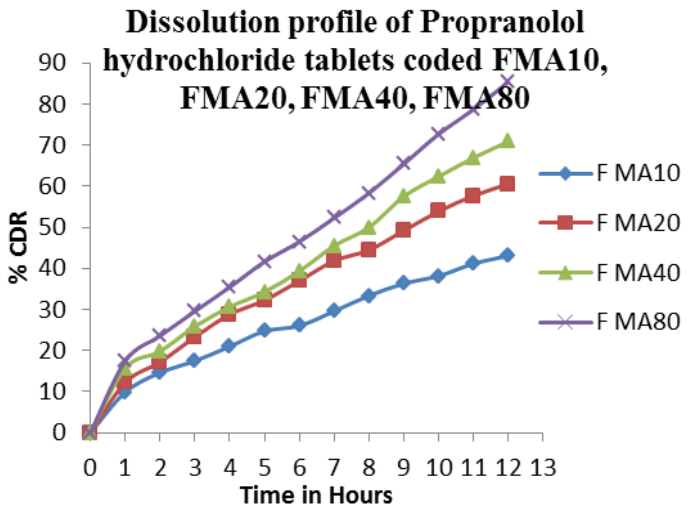

Fig.6: In vitro release rate profile of PPL HCl (10,20,40,80 mg of Maleic acid as a release modifier) in Simulated Intestinal fluid (pH 7.4) Drug: polymer ratio 1:3 F MA10, 1:3 F MA20, 1:3 F MA40, 1:3 F MA80

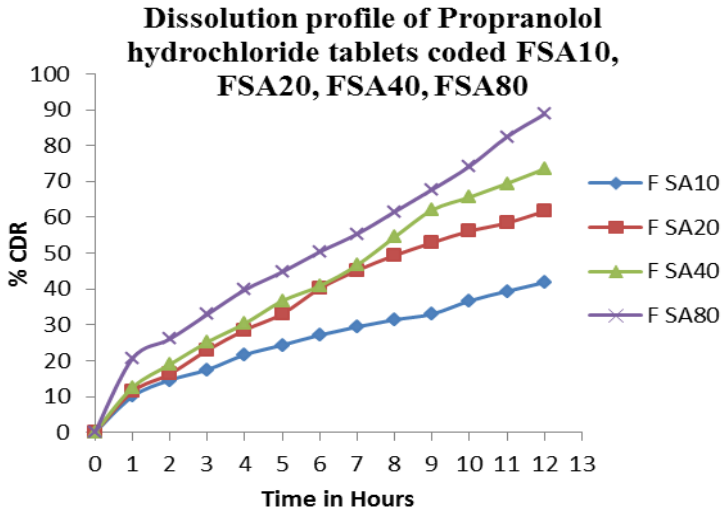

Fig.7 In vitro release rate profile of PPL HCl (10,20,40,80 mg of Maleic acid as a release modifier) in Simulated Intestinal fluid (pH 7.4) Drug: polymer ratio 1:3 F SA10, 1:3 F SA20, 1:3 F SA40, 1:3 F SA80

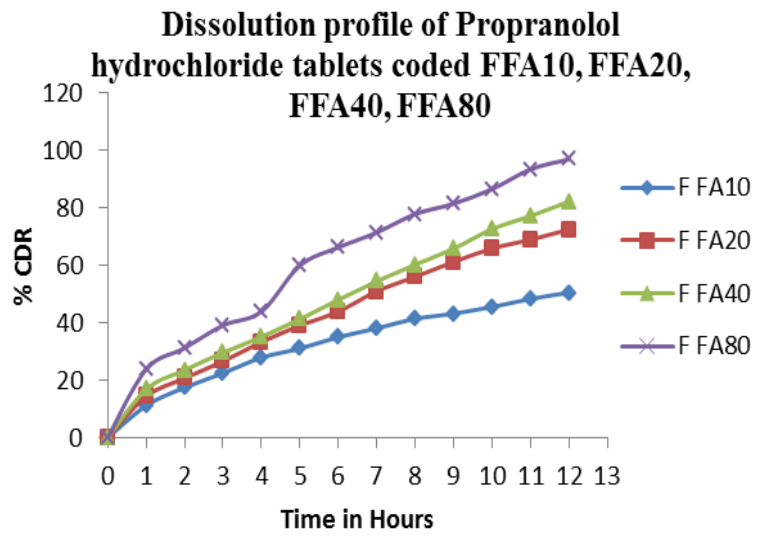

Fig.8 In vitro release rate profile of PPL HCl (10,20,40,80 mg of Maleic acid as a release modifier) in Simulated Intestinal fluid (pH 7.4) Drug: polymer ratio 1:3 F FA10, 1:3 F FA20, 1:3 F FA40, 1:3 F FA80

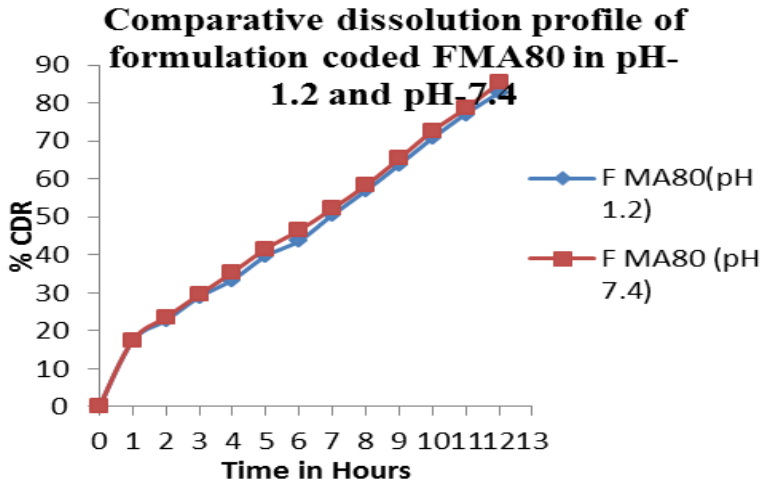

Fig.9 In vitro release rate profile of PPL HCl (80mg of Maleic acid as a release modifier) Simulated gastric fluid (pH 1.2),in Simulated Intestinal fluid (pH 7.4) Drug: polymer ratio 1:3 F MA80.

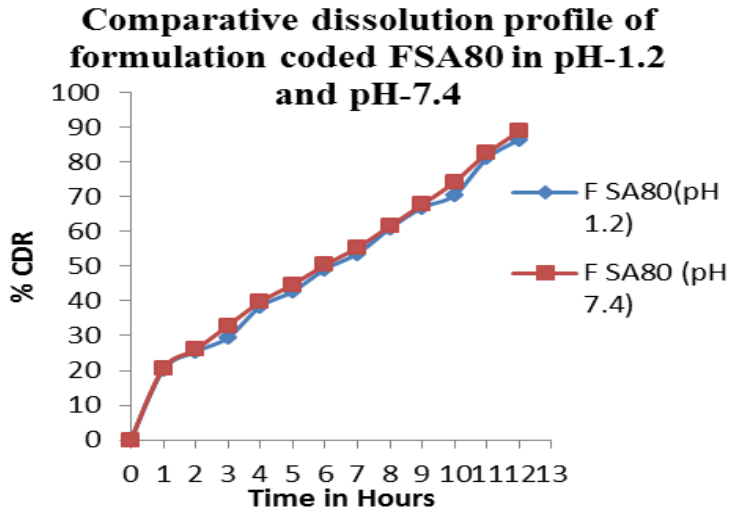

Fig.10 In vitro release rate profile of PPL HCl (80mg of Maleic acid as a release modifier) Simulated gastric fluid (pH 1.2),in Simulated Intestinal fluid (pH 7.4) Drug: polymer ratio 1:3 F SA80.

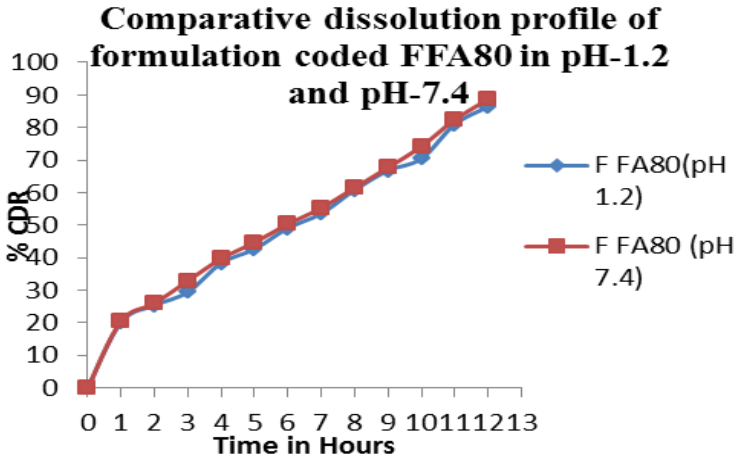

Fig.11 In vitro release rate profile of PPL HCl (80mg of Maleic acid as a release modifier) Simulated gastric fluid (pH 1.2),in Simulated Intestinal fluid (pH 7.4) Drug: polymer ratio 1:3 F FA80.

Without pH-modifier, a very low percentage of drug release from hydrophilic matrix tablets in simulated intestinal fluid is observed during dissolution study. This can be explained by the fact that Propranolol hydrochloride is basic drug with a pKa value of 9.45, or the pH value at which drug precipitation occurs is exceeded by the pH of the SIF, precipitated drug no longer capable of diffusing through the diffusion layer and is therefore not released. This problem has been solved by the addition of organic acids such as maleic acid, succinic acid and fumaric acid to the selected tablet formulation. These organic acids maintain the pH

value low within the core of the tablet; hence a constant drug release can be achieved over a wide pH-range in the environment, depending on the type and amount of organic acid added. Effect of addition of pH-modifiers on the release rate of the drug In the present investigation effect of the some of the pH-modifiers on the release rate of basic drug (Propranolol hydrochloride) is investigated to adjust the release profile of basic drug in phosphate buffer of pH 7.4 comparable to that in pH 1.2.

EFFECT OF ORGANIC ACIDS

This approach was based on the addition of organic acids to create a constant acidic microenvironment inside the tablets. Ideally, these pH-modifiers should dissolve rather slowly to remain within the tablet during the entire period of drug release. The pH is expected to remain acidic inside the tablet matrix independent of the pH of the dissolution medium and thus the solubility of basic drug has to be high. In this case, drug release should be pH - independent. For this purpose, substance with high acidic strength (low pKa) and relatively low solubility in 0.1 N HCl were suitable. Here organic acids such as maleic acid, succinic acid and fumaric acid were selected.

These organic acids also acts as pore-formers at high pH values. The addition of organic acids such as maleic acid, succinic acid and fumaric acid significantly increased the drug release in phosphate buffer of pH 7.4. The resulting release profile at phosphate buffer pH 7.4 almost overlapped with the ones in pH 1.2. This is in good agreement with the hypothesis for a constant micro environmental pH within the tablets.

In this research work three organic acids (maleic acid, succinic acid and fumaric acid) were used in varying ratios (10 mg, 20mg, 40mg, and 80mg). It was also found thatith increase in amount of organic acids added, the drug release rate also increased. Among the three organic acids, fumaric acid showed slightly better release in comparison to succinic acid and maleic acid, because of its low solubility in dissolution media and its low pKa value. Influence of pH of the dissolution media on the release rate of drug The study was carried out by placing the tablets containing release modifiers (organic acids) pH 1.2 (37^0 C at 50 rpm). It is observed that ph of 0.1N HCl did not alter the release rate of the drug.

Different results of this study could be attributed to the type of the polymer and additive used for matrix preparations. It seems that formation of a gel barrier around tablet after hydration of HPMC slows down the diffusion of dissolved organic acid towards out of the matrix

system and keeps it inside the matrix core for a longer period of time. On the other hand, high quantity of soluble additives (such as lactose) of the other study might result in formation of a pore following dissolution, which in turn increases the diffusion of soluble acid out of the matrix. Also, it might enhance the dissolution of less soluble organic acids. It has been emphasized that soluble additives create a more permeable hydrated gel layer, increase the porosity and rate of erosion of HPMC-based tablet, leading to faster solute release.[9]

In this investigation, dicalcium phosphate was used in the matrix preparation which is an insoluble additive and does not show the same effect as lactose during dissolution studies. In order to clarify the mechanism of pHindependency, release matrix tablet based on HPMC containing pelanserin has been prepared[10] by using citric acid and it has been found that the drug release in acidic medium from formulation without citric acid was lower than the one containing citric acid. It has been concluded that increase in the porosity and loosening effect of citric acid in the matrix structure might be the main mechanism for pH-independent release of pelanserin. In this study, there was no significant difference between the MDT values of tablets (containing 30% HPMC) made in the presence of the organic acids and the basic one (without any acid) at pH 1.2. Therefore, the influence of acids on micro-environmental pH and modification of the drug solubility at higher pH seems to be the major pH-independent release mechanism. Pore forming and matrix loosening effects of the soluble organic acids might be observed at higher concentrations.

STABILITY STUDIES

Stability studies were carried out at 25^0C / 60 % RH and 40^0C / 75 % RH for the following selected formulations for 30 days.

- Formulation coded $F_{SA\ 80}$
- Formulation coded $F_{FA\ 80}$

Table 3: Results for the selected formulations stored at 25^0C / 60 % RH.

Time in weeks	Formulation – $F_{SA\ 80}$			Formulation – $F_{FA\ 80}$		
	PA	H	%DC	PA	H	%DC
0	+++	5.0	97.50	+++	5 .0	98.45
4	+++	5.0	96.50	+++	5.0	97.25
8	+++	5 .0	96.01	+++	5 .0	96.58

Table 4: Results for the selected formulations stored at 40^{0}C / 75 % RH.

Time in weeks	Formulation – $F_{SA\ 80}$			Formulation – $F_{FA\ 80}$		
	PA	H	%DC	PA	H	%DC
0	+++	5.0	97.50	+++	5 .0	98.45
4	+++	5.5	97.12	+++	5.5	97.40
8	++	5 .5	96.36	++	5 .5	96.33

PA - Physical Appearance +++ Same as on 0 day

H Hardness (Kg / cm2) ++ slightly change in color

% DC % Drug content

CONCLUSION

In conclusion, a hypothetic matrix system that provides controlled drug release essentially independent of pH & GIT was successfully designed for basic drug by incorporating a release modifier. The addition of an acidic release modifier to matrix former maintained low pH values within the tablet during drug release in simulated intestinal fluid leading to pH independent drug release. From results, it can be concluded that formulation containing fumaric acid proved to be an effective release modifier than the other two formulations containing organic acids such as succinic acid and maleic acid, because of its high buffering capability.

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