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A pH INDEPENDENT SUSTAINED RELEASE DRUG DELIVERY SYSTEM OF PROPRANOLOL HYDROCHLORIDE

R. Sri harshida*, G. Lakshmna murthy*, K. Ruth Vijaya Priyanka

*Department of Pharmaceutics Jagan's College Pharmacy, Nellore, Andhra Pradesh, India.

ABSTRACT

The objective of this research work is to develop a pH independent sustained release drug delivery system for a model drug propranolol hydrochloride basic drug to overcome the decreased bioavalibility and to avoid variation of drug release at various gastro intestinal pH. Organic acids such as succinic acid, maleic acid and fumaric acid were used as release modifiers. In case of formulations without any release modifier, the extent and rate of drug release at pH 1.2 was much higher than that of at pH 7.4. Different formulations were prepared by using release modifiers in different amount in order to overcome the pH dependent solubility. The formulation were subjected to various evaluation parameters such as hardness, friability, assay and *in-vitro* release studies. An in vitro release study was carried out in two different pH Medias such as pH 1.2 and pH 7.4. Through *in-vitro* release studies it was found that formulation containing 80 mg of fumaric acid provided better drug release compared to formulation containing maleic acid and succinic acid. The selected formulations were subjected to stability studies. Finally, it was concluded that propranolol hydrochloride could be formulated as a pH- independent matrix tablet using fumaric acid as a release modifier.

Key Words: Propranolol Hydrochloride, Fumaric acid, Maleic acid, Succinic acid.

Author for correspondence:
G. Lakshmna murthy
Department of Pharmaceutics,
Jagan's College Pharmacy, Nellore,
Andhra Pradesh, India.

Email: murthympharm@gmail.com

INTRODUCTION

Oral route has been the most widely used & most convenient route for the drug delivery. Oral route of administration has received more attention in the pharmaceutical industry and research field because of the flexibility in designing of dosage form & constraints like sterility & potential damage at the site of administration are minimized. The novel drug delivery system involves a new technique of formulation of existing drug substances. In recent years attention has been focused on the development of new drug delivery systems.

The conventional dosage form releases drug rapidly & creates the absorption pool at the site of absorption and thus attains a high plasma drug concentration. Hence, the rate of absorption becomes the rate-limiting step. But in case of sustained release or controlled release dosage forms the drug is released for prolonged period along the entire length of the GIT. Here the rate of release of drug from the dosage form becomes less when compared to rate of absorption. Hence the rate of release of drug becomes the rate-limiting step. The term "sustained release" is used to describe the pharmaceutical dosage form formulated to retard the release of drug such that its appearance in systemic circulation is delayed or prolonged & its plasma profile is sustained. The term "controlled release" on the other hand, has a meaning that goes beyond the scope of sustained dosage form. It also implies a predictability and reproducibility in the drug release kinetics, which means that the release of drug(s) from a controlled release drug delivery systems is not only predictable kinetically but also reproducible from one unit to another (1-6).

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 & inter-individual variability's in bioavailability & this system is useful for increasing bioavailability of drugs. Therefore, pH-independent drug release system is desirable to assure a reliable drug therapy (7-10).

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 & inter individual variability in bioavailability.

MATERIALS AND METHOD

Materials

Propranolol, Hydroxy propyl methyl cellulose, Lactose DC, Magnesium stearate, Hydrochloric acid, Potassium chloride, Maleic acid, Succinic acid and Fumaric acid were purchased from Aurobindo Pharma Ltd. Hyderabad.

Standard graph of Propranolol hydrochloridein simulated gastric fluid (pH 1.2)

Preparation of simulated gastric fluid (pH 1.2): 8.5 ml concentrated hydrochloric acid and 0.8 gm of Sodium chloride was dissolved in 1000 ml of distilled water.

Procedure

50 mg of pure Propranolol hydrochloride was accurately weighed and dissolved in 100 ml of pH 1.2 buffer solution (SS-I, 500 mcg/ml). 10ml of the stock SS-I was

pipetted into another 100 ml volumetric flask and the volume was made up to 100 ml with pH 1.2 buffer solution (SS-II, 50 mcg/ml). From this further dilutions were made. The absorbances were measured at 216 nm against reagent blank (pH 1.2).

In simulated intestinal fluid (pH 7.4)

Preparation of Simulated Intestinal Fluid (pH 7.4): - 50 ml of 0.2M Potassium dihydrogen ortho phosphate was taken in a 200 ml volumetric flask, to this 44.5 ml of 0.2 M NaOH was added and mixed thoroughly and the volume was made up to 200 ml with distilled water.

Procedure: 50 mg of pure Propranolol hydrochloride was accurately weighed and dissolved in 100 ml of pH 7.4 buffer (SS-I, 500 mcg/ml). 10 ml of stock solution-I was pipetted to another 100 ml volumetric flask and the volume was made up to 100 ml with pH 7.4 buffer solution (SS-II, 50 mcg/ml). From this further dilutions were made as given in the table. The absorbances were measured at 216 nm against reagent blank (pH 7.4 buffer).

Formulation

Drug (PPL HCl), polymer, organic acids (maleic acid, succinic acid and fumaric acid) and diluents (lactose DC) were first passed through sieve #.80 and accurate quantity was weighed mixed in geometric proportion using the mortar and pestle followed by lubrication using magnesium stearate (0.5 %) (Table-1). The physical mixture so obtained was subjected to compression using a 10-station 'Remix' minipress tablet punching machine using 8mm diameter flat punches.

The polymer was $HPMCK_4M$ .the hardness for the tablets was maintained at 5 kg/cm^2 in order to compare their in vitro release studies (11, 12).

In vitro release profile

The 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 ^0C □□-0.5 ^0C. 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 50 ml volumetric flask and the volume was made up to the mark with the respective dissolution medium and analyzed by using an UV spectrophotometer (Elico SL-159) against reagent blank. Each time 5 ml of the respective fresh dissolution medium was replaced into the Jar (13).

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.

The selected formulations were packed in amber-colored bottles, tightly plugged with cotton and capped. They were then stored at 25 ^0C / 60 % RH and 40 ^0C / 75 % RH for two months and evaluated for their physical appearance and drug content (13).

RESULTS AND DISCUSSION

The present study was carried out to develop pH-independent controlled release matrix tablet of Propranolol hydrochloride due to variable pH values observed in the GIT. The conventional controlled release matrices of Propranolol hydrochloride showed pH dependent solubility, as a result bio-availability of drug from a controlled release dosage form is greatly affected, to overcome this problem and to achieve pH-independent drug release suitable pH-modifiers are incorporated in the formulation.

Preformulation

Propranolol hydrochloride by UV spectrophotometer method revealed a □λmax at 216 nm in simulated gastric fluid (pH 1.2) as well as in simulated intestinal fluid (phosphate buffer pH 7.4). It obeys beers-lamberts law in the range of 2-18 mcg/ml (Table-2 and Fig-1).

A calibration curve was constructed in the beers range of 2-18 mcg/ml. The correlation coefficient for the standard curve in simulated gastric fluid was found to be 0.9997 & in simulated intestinal fluid was found to be 0.9998. The regression equation generated was y=0.148x- 0.009 in simulated gastric fluid pH 1.2, y = 0.1469x- 0.0086 in simulated intestinal fluid pH 7.4 (Table-3 and Fig-2)

Solubility study

Propranolol hydrochloride is an ideal model of anti-hypertensive drug to test the formulation concept because of its distinct pH-dependent solubility. The solubility study of Propranolol hydrochloride was carried out in buffer solutions having pH 2.0, pH 3.6, pH 6.0 and pH 7.4 respectively. It was found that PPL HCl shows optimum solubility at pH 2.0 when compared with pH 3.6, pH 6.0 and pH 7.4, i.e., it has optimum solubility at pH 2.0 (120.5224 mcg/ml). The solubility decreases to about 71.2462 mcg/ml at pH 6 and it further decreases to 63.5386 mcg/ml and 3.053 mcg/ml at pH 4 and pH 7.4 respectively.

Formulation and evaluation

In the present study, hydroxyl propyl methyl cellulose polymer was used as a matrix former in which the drug, propranolol hydrochloride was embedded. The drug: polymer ratio of 1:3 was selected as an optimized formula for this research work, because it gave a CDR of 27.71 % in simulated intestinal fluid pH 7.4 at the end of 12^{th} hr, based on this observation it was assumed that if same formulation contains the release modifiers in addition to it, it could release approximately 100 % of the drug at the end of 12^{th} hour in simulated intestinal fluid of pH 7.4. To this selected formulation release modifiers such as maleic acid, succinic acid and fumaric

acid were added. The amount of each release modifier added to the selected formulation was 10 mg, 20 mg, 40 mg and 80 mg respectively, hence totally 4x3 = 12 formulations were made.

The tablets were prepared by direct compression method using 8 mm flat punches with brake-line, and the tablets were white in color. No chipping or breakage of tablets was observed during compression and also during storage. The formulations were subjected to various precompression parameters and post compression parameters.

Precompression parameters

The precompression parameters like bulk density, tapped density, angle of repose & Carr's index were studied. Above parameters showed that the prepared physical mixtures were having good flow properties and compression properties required for tablet formulation.

Post compression parameters

The hardness was determined using Monsanto hardness tester for all the formulations. The hardness of all the formulations was kept at 5.0 □ 0.2 kg/cm^2 to compare the release profile between the formulations.

The percentage friability of all the formulations was found to be not more than 0.255 %, which is well within the 1% limit. The results of friability indicated that the tablets were mechanically stable.

The weights of the tablets were between 245.0 mg to 255.0 mg. As the weight of tablets was 250 mg, the acceptable weight variation range is between 245.0 mg to 255.0 mg.

Hence, all the tablet formulations passed the weight variation test, as per IP specification for a 250 mg tablet (14).

Assay

The drug content of all the tablets was found to be between 93.31 % and 101.21 % of the label claim of Propranolol hydrochloride, which was within the acceptable limits (14, 15).

In-vitro release study

The In vitro release rate study was carried out in two different 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 F_5 revealed a CDR of 25.02 % at the end of 5 hrs in pH 1.2, where F resulted with a CDR of 15.34 % at the end of 5 hrs in pH-7.4. Formulation F_5 revealed a CDR of 53.41 % in pH 1.2 and 27.71 % in pH 7.4 at the end of 12 hrs. 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-3).

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.

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. 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 act 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 that with 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 (Fig-4).

Table-1 HPMCK_4M based formulation without organic acid coded F_1, F_2, F3, F4, and F5

Sl. No	INGREDIENTS*	F_1	F_2	F_3	F_4	F_5
1	Propranolol hydrochloride	38.0	38.0	38.0	38.0	38.0
2	HPMC 4000CPS	38.0	57.0	76.0	95.0	114.0
3	Lactose DC	172.5	153.5	134.5	115.5	96.5
4	Magnesium stearate	1.5	1.5	1.5	1.5	1.5
5	Total	250	250	250	250	250

Table-2 Data for standard curve of PPL HCl in simulated gastric fluid pH 1.2 buffer solutions.

Vol. SS-II(ml)	Vol. dil.	Conc. mcg/ml	Absorbance at 216 nm			Avg	SD	SEM
			Trial - I	Trial -II	Trial III			
1	25	2	0.298	0.305	0.300	0.301	0.0032	0.0018
2	25	4	0.604	0.608	0.603	0.605	0.0023	0.0013
3	25	6	0.909	0.914	0.910	0.911	0.0023	0.0013
4	25	8	1.197	1.201	1.196	1.198	0.0023	0.0013
5	25	10	1.495	1.500	1.996	1.497	0.2574	0.1488
6	25	12	1.766	1.771	1.767	1.768	0.0023	0.0013

Table-3 Data for standard curve of PPL HCl in simulated Intestinal fluid pH 7.4 buffer solution

Vol. SS-II (ml)	Vol.dil.	Conc. mcg/ml	Absorbance at 216 nm			Avg	SD	SEM
			Trial - I	ial -II	Trial III			
1	25	2	0.300	0.304	0.299	0.301	0.0026	0.0015
2	25	4	0.612	0.617	0.613	0.614	0.0026	0.0015
3	25	6	0.882	0.889	0.884	0.885	0.0036	0.0020
4	25	8	1.186	1.191	1.189	1.190	0.0025	0.0014
5	25	10	1.469	1.474	1.470	1.471	0.0026	0.0015
6	25	12	1.770	1.774	1.769	1.771	0.0026	0.0015

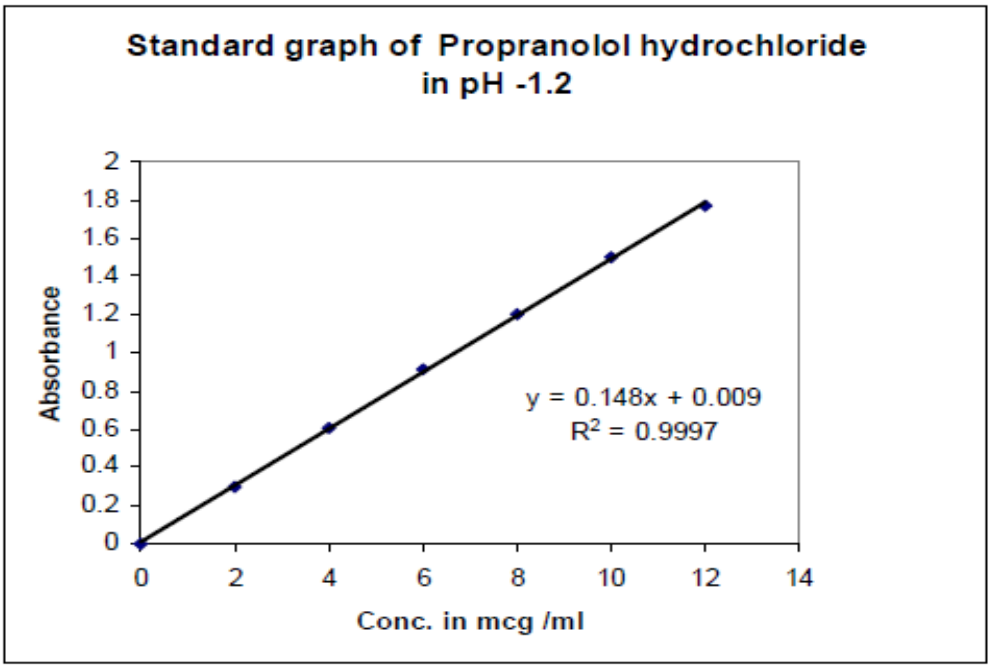

Fig-1 Calibration curve of propanolol hydrochloride in pH 1.2

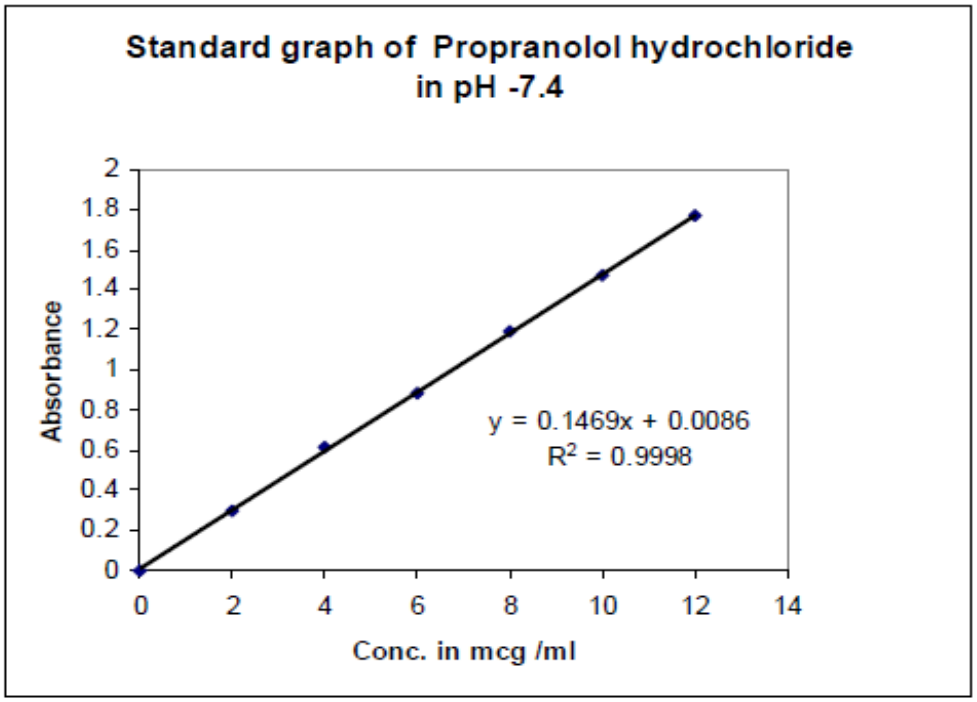

Fig-2 Calibration curve of propanolol hydrochloride in pH 7.4

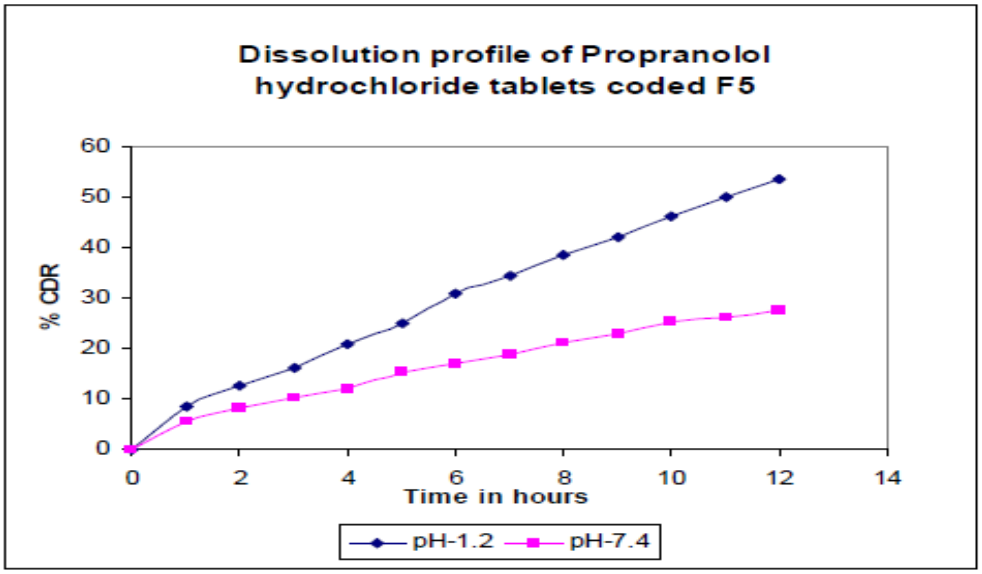

Fig-3 Dissolution profile of propanolol hydrochloride

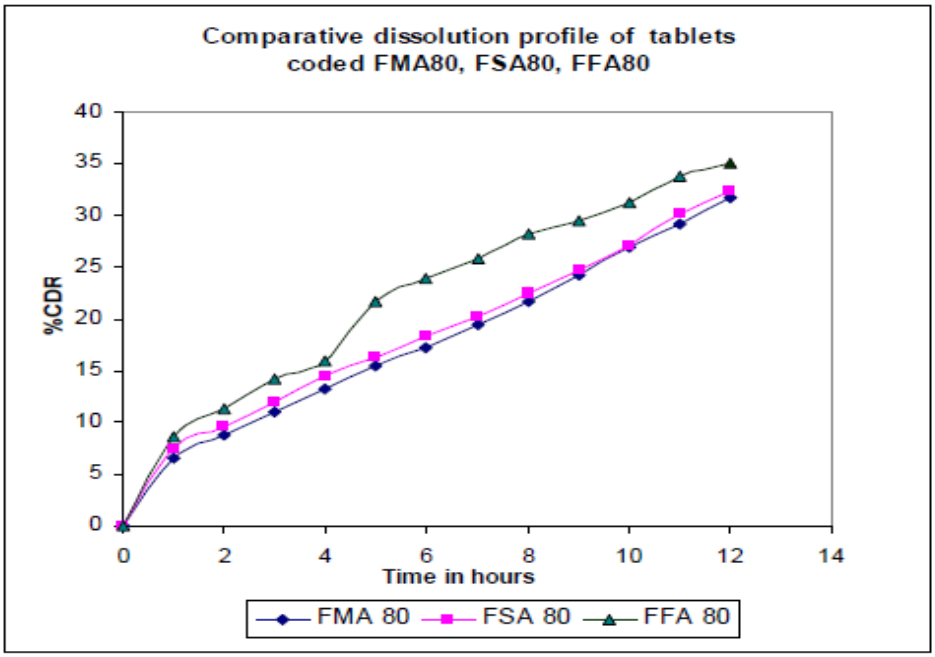

Fig-4 Comparative dissolution profile of tablets

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 & Maleic acid, because of its high buffering capability.

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