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Development of Enteric Coated Sustained Release Matrix Tablets of Sertraline Hydrochloride

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ABSTRACT

The aim of the present investigation is to develop enteric coated sustained release matrix tablets of Sertraline hydrochloride (STH) using HPMC K4M and Carbopol-971 as drug release retardants and cellulose acetate phthalate (CAP) as an enteric coat polymer. The tablets were prepared by direct compression process and evaluated for various physico-chemical/mechanical parameters. Among the two release retardants, HPMC K4M was selected based on controlling the STH release during dissolution. The effect of different fillers like microcrystalline cellulose (MCC), di calcium phosphate (DCP), spray dried lactose with maize starch (SDL) and pre gelatinized starch (PGS), on STH release was also studied. The percent of STH released at the end of dissolution with different fillers is in the order of SDL > MCC > DCP > PGS. The tablets containing 15% w/w of HPMC K4M & MCC as filler with 5% coating weight gain (1% v/v glycerine in 5%w/v CAP solution) gave a STH release of less than 10% in 0.1N HCl (pH 1.2) for 2 h and a sustained release of STH over a period of 12 h (99.17±0.54%) in pH 6.8 phosphate buffer and fulfilled the regulatory requirements. The dissolution data was also evaluated for drug release kinetics and mechanisms.

INTRODUCTION

Sertraline hydrochloride (STH) is primarily selective serotonin reuptake inhibitor (SSRI) belongs to the class of anti-depressant drug and anorectic agent categories. It is most commonly prescribed for the therapy of depressive illness in the dose range of 25-200 mg. Presently, STH is marketed as immediate release (IR) tablets (25, 50, 100 mg) and oral concentrate (20mg/mL). Severe side effects like nausea; regurgitation and diarrhea which are partially or primarily mediated by direct contact of STH with the upper GIT, preferably stomach were observed with higher doses (Am Ende, 2003). Hence, delivery of STH in a dosage form which minimizes the gastric exposure is necessary to reduce the dose related side effects in the upper GIT and release STH in the small intestinal region. STH when released in the small intestinal region may exhibit faster onset of action with shorter T_{max} due to efficient absorption (Curatolo, 2003). Moreover, the sustained release (SR) in small intestine may enhance the absorption of STH and results in improved therapeutic efficacy by shorter onset of action. So far, till to date no reports were published on STH enteric coated SR matrix tablets. Hence, the aim of the present study is to develop enteric coated SR matrix tablets of STH to achieve better therapeutic efficacy and more patient compliance when compared to marketed IR tablet dosage forms.

MATERIALS AND METHODS

Materials

Sertraline hydrochloride was obtained from Alekhya Laboratories, Vijayawada, India as a gift sample. Cellulose acetate phthalate was obtained from Sisco Research Laboratories Pvt.Ltd, Mumbai. HPMC K4M was obtained from Colorcon, India. Carbopol-971 was obtained from Lubrizol polymers, Belgium. Partially pre gelatinized starch, spray dried lactose with maize starch were obtained from Roquette Pharma, France. Dicalcium phosphate was obtained from Finar, Mumbai, India. Micro-crystalline cellulose (Avicel PH 101) was obtained from FMC biopolymer, USA. Talc and magnesium stearate were obtained from Loba Chemie, India. All other reagents used were of analytical grade.

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Solubility Studies of STH

Buffers of pH 1.2 acidic (0.1N HCl), pH 4.5 acetate and pH 6.8 phosphate were used to study the solubility of STH. Excess of STH was added to 10mL of buffer taken in a 15mL stopper conical flask and shaken well for 24 h on a rotary flask shaker at room temperature. After 24 h, samples were withdrawn and filtered through 0.45µ nylon disc filters. These filtrates were diluted suitably with buffer and measured at an absorbance of 213 nm (UV-VIS spectrophotometer, UV-1800-Shimadzu). The solubility studies were carried out in triplicate.

Drug-Excipient Compatibility Studies

FTIR

The FT-IR spectra of STH and STH with different excipients like HPMC K4M, MCC, SDL, PGS, DCP, CAP, citric acid, magnesium stearate and talc was measured using ATR-FTIR spectrophotometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000–500 cm^{-1} at a resolution of 1.0 cm^{-1}. The powder sample is simply placed onto the ATR crystal and the sample spectrum is collected.

DSC

Thermal analysis of pure STH and STH with selected excipients like HPMC K4M, MCC, DCP, SDL, PGS, magnesium stearate, talc and CAP was performed using DSC (DSC 200F3 Maia, Netzsch). The sample was sealed in a crimped aluminum pan by application of the minimum possible pressure and heated at a rate of 10 ºC /min from 30-300 ºC in a nitrogen atmosphere. An empty aluminum pan was utilized as the reference pan.

Preparation of STH SR Tablets by Direct Compression Technique

STH SR Matrix tablets were prepared by direct compression method, as per the formulae given in Table 1. All the ingredients were passed through sieve # 80 before mixing. Initially drug and polymers were mixed thoroughly and then required quantities of fillers were added and then the blend was mixed with talc thoroughly for 5min in a poly bag and then finally added the required amount of magnesium stearate and mixed for another 5 min. Powder blends (for 50 tablets each) of all the formulations were compressed on single punch tablet press (Cad mach, India) using 10 mm punches (round shape) to a hardness of 4-6 kg/cm^2.

Enteric Coating of SR Tablets

The core tablets were coated with CAP by dip coating method and the coating solution formulae were given below. In dip coating method, the tablet cores were dipped into the coating solution in a beaker and then wet tablets were dried in a conventional manner by hot air blower. Coating was repeated until the target coat weight was achieved. 5%w/v CAP in Acetone: Methanol (50:50 v/v) solvent mixture was used for enteric coating of F3 SR matrix tablets using different plasticizers like Glycerine, PG and PEG-400 in coating solution (Table 2).

5% w/v of Cellulose Acetate Phthalate in Acetone

Methanol (50:50) solvent mixture was prepared with addition of 1%v/v plasticizer (Glycerine or Propylene Glycol or Polyethylene Glycol). Precaution was taken always that CAP should be added to the solvent to make coating solution.

Evaluation of Pre Compression Parameters of the Powder Blend

Pre compression parameters like bulk density, tapped density, compressibility index, hausner's ratio and angle of repose of the prepared powder blend of all the formulations were studied.

Evaluation of Post Compression Parameters of STH Tablets

The compressed STH tablets were subjected to various physical tests which include hardness, friability, weight variation and drug content uniformity etc.

Table 1: Composition of STH SR Matrix Tablets.

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
STH	28	28	28	28	28	28	28	28	28	28
HPMC K4M	20	24	30	-	10	30	30	30	30	30
CARBOPOL-971	-	-	-	30	20	-	-	-	-	-
MCC	150	146	140	140	140	130	136	-	-	-
DCP	-	-	-	-	-	-	-	140	-	-
SDL	-	-	-	-	-	-	-	-	140	-
PGS	-	-	-	-	-	-	-	-	-	140
Citric Acid	-	-	-	-	-	10	4	-	-	-
MagnesiumStearate	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1
Total weight (mg)	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Table 2: Enteric coating solution formulations.

Coating solution	Formulations			
	F11	F12	F13	F14
CAP	5%w/v	5%w/v	5%w/v	5%w/v
Acetone: Methanol	50:50 v/v	50:50 v/v	50:50 v/v	50:50 v/v
Glycerine	1%v/v	1%v/v	-	-
1% PG	-	-	1%v/v	-
1% PEG	-	-	-	1%v/v
% Coat weight gain to the core	10%	5%	5%	5%

Hardness

The hardness of the tablets was measured with a Monsanto hardness tester (M/s Campbell Electronics, model EIC-66, India). The results reported were average of 6 tablets for each formulation.

Friability

For each formulation 10 tablets were weighed, placed in friabilator (M/S Campbell Electronics, India) and were subjected to 100 rotations in 4min. The tablets were reweighed and friability was calculated by the following formula:

$$Friability = \frac{W_2 - W_1}{W_1} \times 100$$

Where W_1 is the initial weight and W_2 is the final weight of the tablets.

Weight Variation

The individual and total weight of 20 tablets from each batch was determined. Percentage deviation of the individual weights from the average weights was calculated.

Drug Content

Ten tablets were weighed individually; these were placed in a mortar and powdered with a pestle. Accurately weighed powder sample equivalent to 20 mg of STH was transferred into a 20 ml volumetric flask and made up to volume with pH 6.8 phosphate buffer. The contents of the volumetric flask were sonicated for 15 min in-order to extract the drug into pH 6.8 phosphate buffer. The solution was then filtered, suitably diluted with pH 6.8 phosphate buffer and absorbance was measured at 213 nm using UV-VIS spectrophotometer (UV-1800-Shimadzu). The estimation was carried out in triplicate.

In Vitro Drug Release Studies

In vitro drug release studies of STH SR tablet formulations were carried in 900 mL of pH 6.8 phosphate buffer as dissolution medium using USP type II (Paddle method) Dissolution Rate Test Apparatus (LABINDIA, DS 8000) at 50 rpm. Whereas, in case of enteric coated tablets, dissolution was carried out in pH 1.2 acidic buffer (0.1N HCl) for initial 2 h and remaining time in pH 6.8 phosphate buffer. The temperature was maintained constant at 37±0.5°C.

At predetermined time intervals, 5 mL of sample was withdrawn from the dissolution medium and replacedwith equal volume of fresh medium. After filtration and appropriate dilution, the samples were analyzed at 213 nm for STH content against blank using UV-Visible spectrophotometer. The dissolution experiments were conducted in triplicate.

Release Kinetics and Mechanism

The release kinetics of the STH was studied by plotting the results of the *in vitro* drug release study with various kinetic models like Zero-order (cumulative percent drug release vs. time) (CS Brazel, 2000), First-order (log cumulative percent drug release vs. time) (Lapidus H, 1966), Higuchi's kinetics (cumulative percent drug release vs. √time) (Higuchi T, 1963), and the Korsmeyer and Peppas equation (log cumulative percentage of drug release vs. log time) (Korsmeyer RW, 1983).

RESULTS AND DISCUSSION

Solubility of STH in Different pH Buffers

Solubility of STH in various pH buffers like pH 1.2 acidic (0.1N HCl), pH 4.5 acetate and pH 6.8 phosphate was studied. This study was carried out with a view to select the suitable dissolution medium for STH.

The solubility of the STH in pH 4.5 acetate buffer was found to be more when compared with pH 1.2 and pH 6.8 phosphate buffers (Figure 1). Even though, solubility of STH is less in pH 6.8 phosphate buffer, when compared to the pH 1.2 and 4.5 buffers, the pH 6.8 phosphate buffer was selected as a dissolution medium based on the good solubility of enteric coat polymer CAP in pH 6.8 phosphate buffer when compared to other buffers. Moreover, sink conditions can be maintained with pH 6.8 phosphate buffer.

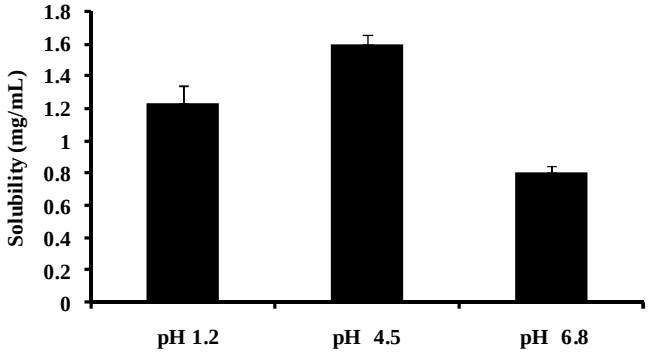

Fig. 1: Solubility of STH in various pH buffers.

FTIR Studies

FTIR spectroscopy was employed to find out the *in situ* compatibility of the STH with the selected excipients. Pure STH showed characteristic IR absorption bands at 902 cm^{-1}, 1211 cm^{-1}, 1369 cm^{-1}, 1740 cm^{-1}, 2971 $cm^{-1}$and 3461 cm^{-1} of aromatic C-H group, C-N group, C-H alkane group, methyl bonded NH_2 deformation, C-H stretching of N-bonded CH_2 group and N-H group respectively.

These significant bands of STH were also present in the IR spectra of physical mixtures of STH with various excipients and thus, revealing the compatibility of STH with the selected excipients (Figure 2).

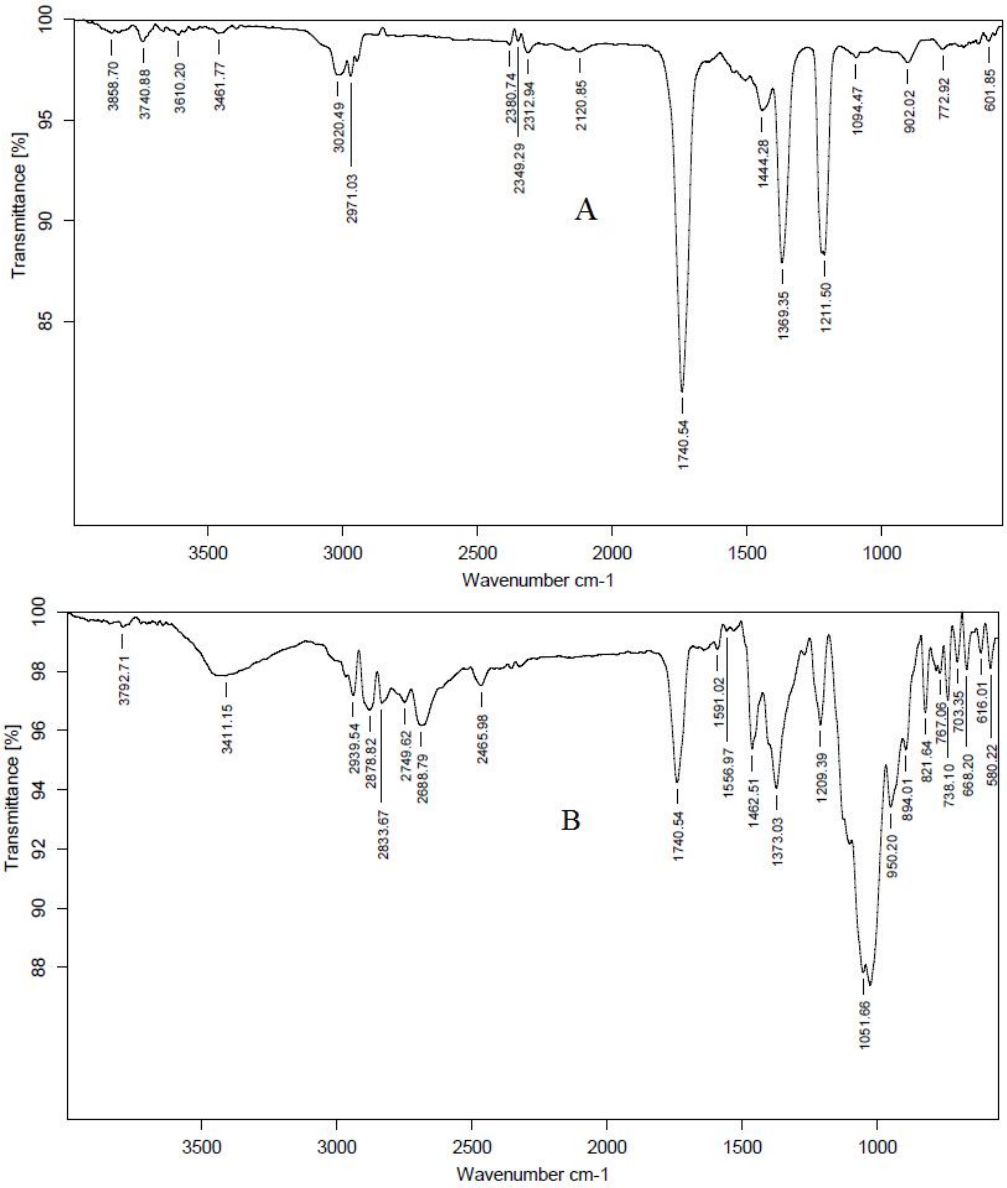

Fig. 2: FTIR spectra of STH (A) and F12 (B).

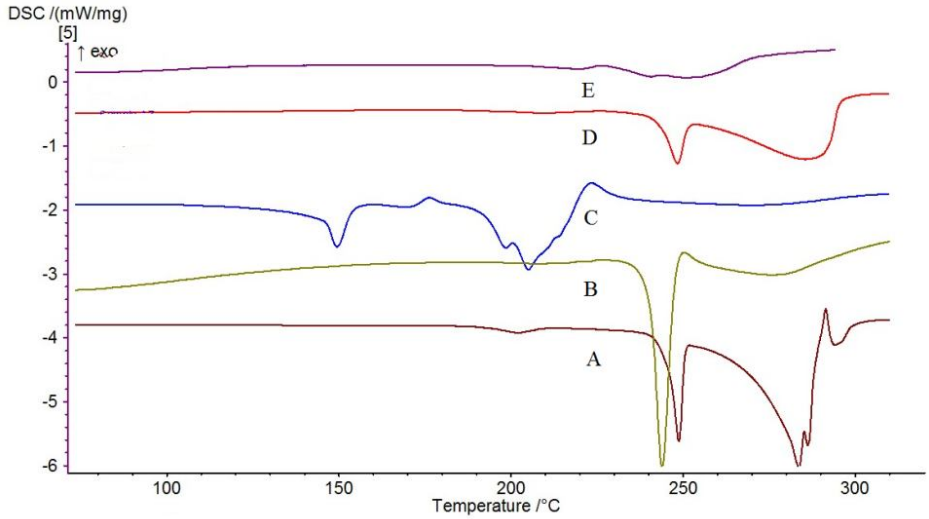

Fig. 3: DSC thermograms of STH (A), STH-PGS (B), STH-SDL (C), STH-DCP (D) and F12 (E).

DSC Studies

DSC thermo grams of the STH alone and STH with the selected excipients were shown in Figure 3. The STH showed a sharp endothermic peak at around 248º C corresponding to its melting point. The sharp endothermic melting peak of STH at 248 ºC was retained in all the thermo grams of STH with selected excipients and optimized formulation except with the SDL (peak shifted to lower melting point). In the case of SDL, the STH melting peak was shifted to 205 ºC and indicating a potential interaction of SDL with STH. Whereas, STH was compatible with all other excipients selected. However, in the case of optimized formulation, the STH peak intensity was reduced due to presence of less amount of STH.

Determination of Pre and Post Compression Parameters

The results of various pre compression parameters indicate that the powder blends of all formulations can be suitable to prepare tablets by direct compression technique. The compressed tablets fulfilled the official compendia requirements regarding drug content, uniformity of weight, hardness and friability.

In Vitro Drug Release Studies

Effect of Release Retardant Concentration on STH release

Initial formulation studies were carried out to look into the release retarding effect of HPMC K4M, at levels of 10-15% w/w in the formulation using MCC as filler.

F1 containing 10% w/w HPMC K4M as a release retardant and MCC as filler gave a 65.87 ± 0.64% initial burst release of STH at 1 h and 99.56 ± 0.24% at the end of 4 h. F2, containing 12% w/w HPMC K4M as a release retardant with MCC as filler gave 49.70 ± 1.467% initial burst release of STH at 1 h and 99.71 ± 0.236% at the end of 6 h and compared to F1 the STH release was extended to another 2 h i.e. for 6h. Concentration of HPMC K4M was further increased to 15% w/w with MCC as filler in F3, resulted initial burst release of 42.07 ± 0.12% at 1h and a complete release of STH i.e. 99.71 ± 0.23% at the end of 10 h. Comparative dissolution profile of F1, F2 and F3 was shown in Figure 4A.

Further trials were carried out using Carbopol-971 at a concentration of 15% w/w and MCC as filler with F4. A 63.76 ± 0.83% STH release of at the end of 12 h with an initial burst release of 9.59 ± 0.11% at 1h. Whereas, in F5, instead of 15% w/w Carbopol-971, combination of Carbopol-971 and HPMC K4M at 10 and 5% w/w respectively with MCC as a filler resulted an initial burst release of 3.73 ± 0.12% and 19.31 ± 1.04 % at the end of 12 h. The STH release from F5 is significantly lower when compared to F3 and F4 at the end of 12h. Comparative dissolution profile of F3 and F4 was shown in Figure 4B. Overall, addition of HMPC K4M didn't increase the STH release when compared to Carbopol-971 alone. Further trials were carried out using 15% w/w of HPMC K4M as release retardant and MCC as filler.

F6 containing MCC as filler, 5% w/w citric acid and 15% w/w HPMC K4M as release retardant gave an initial burst release of 51.94 ± 2.21% and a complete STH release of 99.14 ± 0.48% at the end of 6 h. Whereas, with F7 containing 2% w/w citric acid, an initial burst release of 45.39 ± 1.68% and a complete release (99.43 ± 0.415 %) at the end of 8 h was achieved. Comparative dissolution profile of F6 and F7 was shown in Figure 5. These results indicated that decrease in the citric acid levels showed lesser % of STH release from matrix tablets. This is because citric acid acts as an acidifying agent that may influences the micro environmental pH within the tablet core and increases the solubility of STH in intestinal fluids (Bolourchian, 2008). Even though, the F6 and F7 showed a good initial burst release and complete release of STH, the reproducibility of hardness is troublesome in the presence of citric acid with different batches prepared. Hence, further trials were carried out with F3 to evaluate the effect of fillers on STH release from the SR tablets.

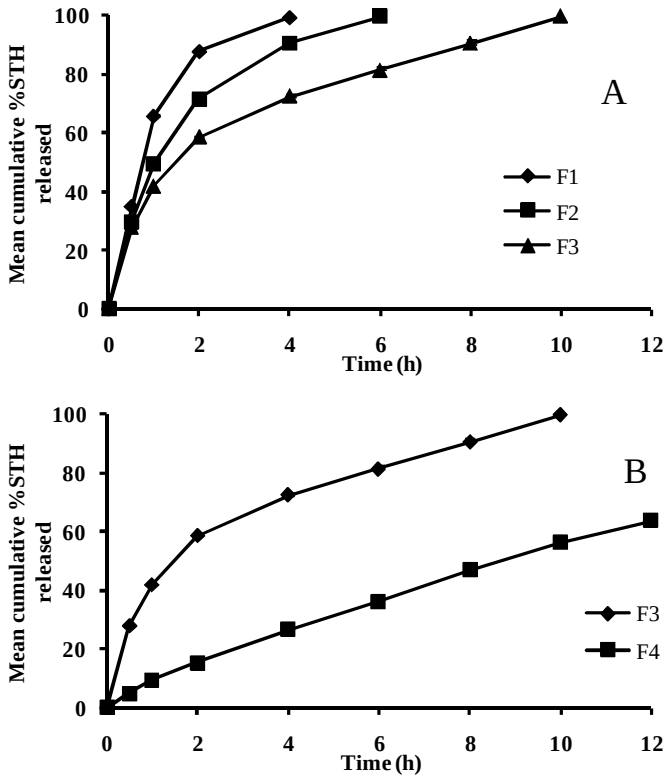

Fig 4: Comparative *in vitro* drug release profiles of STH (A) different concentrations of HPMC K4M (F1, F2 & F3); (B) HPMC K4M (F3) and Carbopol-971 (F4)

Effect of Fillers on STH Release from SR tablets

All the formulations were prepared with 15% w/w HPMC K4M as a release retardant. F8 containing DCP as filler gave an initial burst release of 26.87 ± 0.49% STH at 1 h and a complete STH release i.e. 99.43 ± 0.40% at the end of 10 h. This is due to lower swelling capacity of DCP when compared to MCC.

F9 containing SDL as filler gave an initial burst release of 43.16 ± 0.41% STH at 1 h and a complete release i.e. 99.42 ± 0.42 % at the end of 6 h and the tablets were completely dissolved. This could be due to water soluble nature of SDL and thereby

making the channels in gel matrix. However, SDL was not preferred in further developmental studies; since the STH is incompatible with SDL. F10 containing PGS as filler gave an initial burst release of 10.50 ± 0.19% STH at 1 h and 68.53 ± 0.635% at the end of 12 h and is may be due to the insoluble nature and lower swelling capacity of PGS. The tablets were intact and gel layer remained even at the end of 12 h.

Overall, the initial burst release of STH at 1 h was in the order of SDL > MCC > DCP > PGS with 15% w/w HPMC K4M as a release retardant. F8 containing DCP as filler showed complete STH release within 10 h as like F3, however, the initial burst release observed with the F3 was higher i.e. 42.07 ± 0.12% when compared to F8 i.e. 26.87 ± 0.49%. The release retarding effect of 15% w/w HPMC K4M in the presence of different fillers is in the order of PGS> DCP> MCC> SDL. Comparative dissolution profile of F3, F8, F9 and F10 was shown in Figure 6 A.

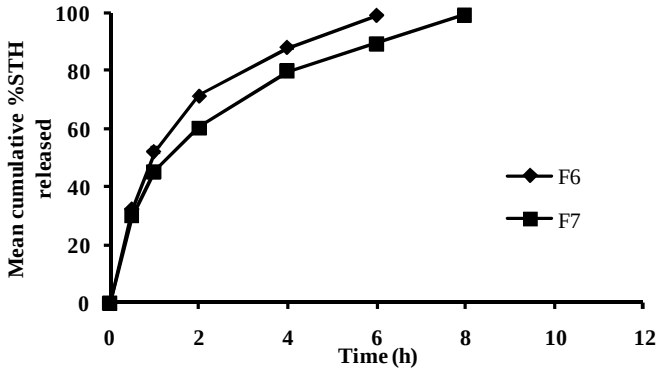

Fig. 5: Comparative *in vitro* drug release profiles of STH with different concentrations of citric acid- F6 (5%w/w) and F7 (2%w/w)

Overall, the formulation F3 containing 15% w/w HPMC K4M as a release retardant with MCC as filler gave complete STH release at the end of 10 h in a sustained release manner with an initial burst release of 42.07 ± 0.12 %. Based on these results, F3 was selected for enteric coating trials. *In vitro* release studies of F3 were also carried out only in pH 1.2 acidic buffer (0.1N HCl) up to 12 h (F3*) and also in pH 1.2 acidic buffer (0.1N HCl) for initial 2h and up to 10 h in pH 6.8 phosphate buffer (F3**) for comparison. F3* gave an initial burst release of 46.59 ± 1.18% and a complete STH release within 8 h (99.03 ± 0.68%). Whereas, F3** gave an initial burst release of 62.14 ± 1.03 % at 2 h and 99.28 ± 0.70% at the end 10 h. From the above dissolution data, F3 was further selected for enteric coating trials with cellulose acetate phthalate (CAP) in order to achieve less than 10% STH release, in the stomach region and complete release in the intestinal region.

Effect of Plasticizers in Enteric Coating Solution on STH Release from Coated SR Tablets

5% w/v CAP solution with 1%v/v Glycerine as plasticizer was tried initially (F11) with a 10% coating weight gain and gave a STH release of 6.05 ± 0.16% in pH 1.2 acidic buffer (0.1N HCl) at 2 h and 80.28 ± 0.15% at the end of 10 h in pH 6.8 phosphate buffer. Whereas, F12 with a 5% coating weight gain gave a STH release of 9.44 ± 0.16% at 2 h in pH 1.2 acidic buffer (0.1N HCl) and 99.17 ± 0.54% at the end of 10 h in pH 6.8 phosphate buffer. The superior dissolution profile observed with the F12 is may be because of low thickness of the enteric coating layer on SR tablets and further trials were carried out with 5% weight gain of the coating solution.

Further trials were carried out by replacing the plasticizer with PG in order to evaluate the affect on STH release. F13 with 1%v/v PG as plasticizer in coating solution gave a STH release of 18.20 ± 0.65% in pH 1.2 acidic buffer (0.1N HCl) at 2 h and 99.55 ± 0.32% at the end of 10 h in pH 6.8 phosphate buffer. Higher % of STH released in pH 1.2 acidic buffer (0.1N HCl) for initial 2 h was due to less viscosity nature coating solution when PG was added when compared to glycerine and not fulfilled the compendial requirement for enteric coated tablets i.e. less than 10% in 2 h in pH 1.2 acidic buffer (0.1N HCl).

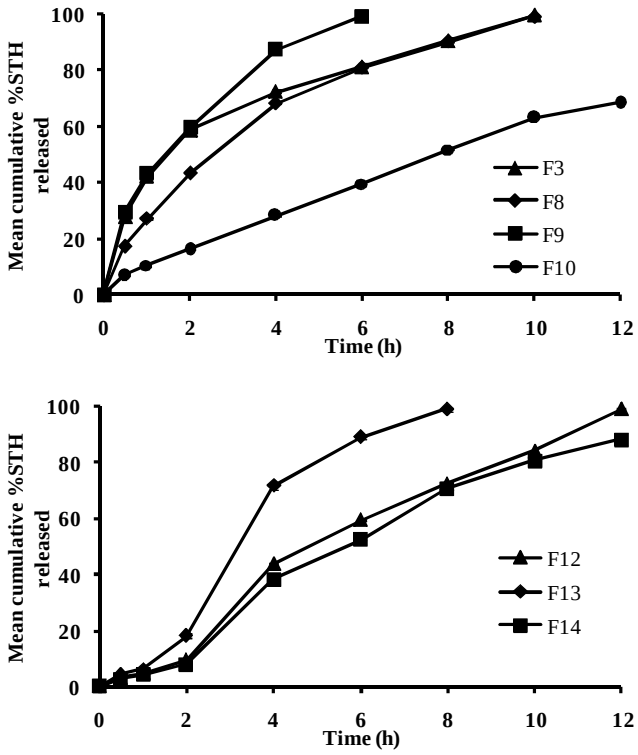

Fig. 6: Comparative *in vitro* drug release profiles of STH using different fillers (A) and enteric coated tablets with different pasticizers- F3 (MCC), F8 (DCP), F9 (SDL) and F10 (PGS), F12 (Glycerine), F13 (PG) and F14 (PEG-400)

Whereas, F14 with 1%v/v PEG-400 as plasticizer gave a STH release of 7.97 ± 0.22% in pH 1.2 acidic buffer (0.1N HCl) at 2 h and 88.50 ± 0.56% at the end of 10 h in pH 6.8 phosphate buffer. The lower STH release at the end of 12 h is may be because of the high viscous nature of PEG when compared to the glycerine and PG. Comparative dissoltion profiles of F12, F13 and F14 were shown in Figure 6 B. Overall, F12 (enteric coated formulation containing Glycerine as a plasticizer with 5% coating

weight gain) gave STH release < 10% in pH 1.2 acidic buffer (0.1N HCl) and complete release of STH within 12 h and has fulfilled the regulatory requirements in terms of percent drug release (i.e. not less than 85% at the end of dissolution studies i.e., 12 h) and also fulfilled the compendial requirement for enteric coated tablets i.e. less than 10% in 2 h in pH 1.2 acidic buffer.

Drug Release Kinetics and Mechanism

The R^2 values for F1-F10 obtained with first order plots were found to be superior when compared to the R^2 values obtained with zero order plots**.** These results indicated that the STH release from F1-F10 followed first order kinetics. The Higuchi square root model showed higher correlation coefficient values (0.894-0.996) and diffusion is the release mechanism for STH from tablets. The graphs of Log Q_t/Q *versus* Log t showed a linear relationship with R^2 values ranged from 0.993-1 and 'n' values from 0.463-0.772. The formulations showed values of n >0.45 but < 0.89, indicating anomalous transport as the release mechanism which includes both swelling and erosion.

CONCLUSION

From the results obtained, it can be concluded that enteric coated sustained release matrix tablets of STH can be successfully formulated using HPMC K4M as release retardant and MCC as filler (F3) with an enteric coat CAP formulation containing glycerine as a plasticizer with 5% coating weight gain. This formulation may minimizes the side effect profile observed with higher doses and also to achieve faster onset of action for better patient compliance when compared to existing marketed dosage forms i.e., immediate release tablets.

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