Formulation and evaluation of enteric coated sustained release matrix tablets of Duloxetine hydrochloride

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ABSTRACT

The present study was aimed at developing enteric coated–sustained release formulation by direct compression for Duloxetine HCl as it lacks the ability to sustain its chemical integrity or stability in acidic gastric environment. Attempts were made to impart the sustained release property by employing HPMC K4M, Sodium Carboxy Methyl Cellulose and Sodium Alginate at drug-polymer ratios 1:1 and 1:0.75. In order to increase the stability at low pH trials were performed by employing 5% CAP as the coating polymer and by the varying the thickness of the coating layer. Initially 5% of the coating polymer was used which resulted in no substantiate increase in stability; the amount of drug release in gastric environment after 2 hrs was found to be greater than 10 %(F1-F3). As a result of this the thickness of the coating polymer was increased by two folds, favourable decrease in the release was observed (F4-F9).Finally it was found in the further trial that the drug release was around 6 -7 % when the coating layer thickness was increased to 20 %(F10-F15).The cumulative release for all the formulations (F1-F15) after 10 hrs in 6.8 phosphate buffer were reported be in compliance with compendial specifications.

Key words: Duloxetine HCL, enteric coated tablets, sustained release.

INTRODUCTION

Duloxetine HCL is a low solubility & high permeability, anti-depressant drug according to the BCS system (Class II). Chemically it's called (+)-(*S*)-*N*-Methyl-γ-(1-naphthyloxy) -2- thiophenepropylamine hydrochloride. Duloxetine is a selective SNRI (selective serotonin-norepinephrine reuptake inhibitor). Duloxetine is a systemic drug therapy which affects the body as a whole. It is a potent dual reuptake inhibitor of serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE), possessing comparable affinities in binding to NE- and 5-HT transporter sites. The saw-tooth pattern of plasma drug concentrations following oral drug administration is associated with adverse events at maxima ("peaks") and loss of therapeutic effect at minima ("troughs") that have led to intolerability or frequent dosing of many antidepressants as is the case with Duloxetine HCl.

Sustained-release formulations of antidepressant agents have the potential to improve tolerability by reducing adverse effects early in the course of therapy a critical period of dramatic dropout. By lowering the peak plasma drug concentrations inherent to the immediate release formulations, side effects for sustained-release formulations can frequently be reduced to more acceptable levels. Duloxetine is highly unstable in acidic environment (gastric pH). In therapeutic dosing with Duloxetine tablets, the drug release is delayed for two to three hours due to enteric coating. Hence in the present invention enteric coated Sustained Release formulations of Duloxetine hydrochloride were prepared using hydrophilic polymers like HPMC K4M, Sodium carboxy methyl cellulose, Sodium alginate.

MATERIALS AND METHODS

Duloxetine hydrochloride (Gift sample from HETERO labs, Hyderabad), Hydroxyl propyl methyl cellulose k4m, Sodium Carboxy Methyl Cellulose, Sodium Alginate, Cellulose Acetate Phthalate, Methanol, Acetone, Micro Crystalline Cellulose, Magnesium Stearate, Talc, Hydrochloric Acid, Potassium Dihydrogen Ortho Phosphate, Sodium Hydroxide

Distilled Water. Duloxetine hydrochloride core tablets were prepared by direct compression and enteric coating was done by using Cellulose Acetate Phthalate solution prepared by mixing acetone and methanol. The tablets are dried and further proceeded for quality control tests and in-vitro drug release studies.

Stability studies were conducted by following ICH guidelines. FTIR and DSC studies were conducted as a part of stability studies both pre-formulation and post formulation.

Table.1.Formualtion table

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Duloxetine HCl	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
HPMC K4M	30	0	0	30	0	0	22.75	0	0	30	0	0	22.75	0	0
Sodium Carboxy Methyl Cellulose	0	30	0	0	30	0	0	22.75	0	0	30	0	0	22.75	0
Sodium Alginate	0	0	30	0	0	30	0	0	22.75	0	0	30	0	0	22.75
Microcrystalline Cellulose	138	138	138	138	138	138	138	138	138	138	138	138	138	138	138
Talc	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Magnesium Stearate	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Total Weight	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

RESULTS AND DISCUSSION

F1, F2, F3: Matrix Tablets Prepared By Using 5 % Coating Polymer with 5% Coating Layer of CAP (1:1); F4, F5, F6: Matrix Tablets Prepared by Using 5 % Coating Polymer with 10% Coating Layer of CAP (1:1); F7, F8, F9: Matrix Tablets Prepared by Using 5 % Coating Polymer with 10% Coating Layer of Cap (1: 0.75); F10, F11, F12: Matrix Tablets Prepared by using 5 % Coating Polymer with 20% Coating Layer of CAP (1:1); F13, F14, F15: Matrix Tablets Prepared by using 5 % Coating Polymer with 20% Coating Layer of CAP (1:0.75)

***In-Vitro* Drug Release Studies of Duloxetine Hydrochloride Enteric Coated Matrix Tablets Prepared By Using 5 % Coating Polymer with 5% Coating Layer of CAP:** The *in vitro* drug release profiles of Duloxetine hydrochloride from the matrix tablets containing drug, enteric coating polymer and Sustained Release polymers.

The cumulative percent drug release for F1, F2, F3, was at the end of 2hrs of dissolution in 0.1N HCl buffer was found to be 14.18 ± 0.74, 15.04 ± 0.80, 14.07 ± 0.91. The formula F1, F2, F3 showed greater than 10 % of drug release at the end of 2 hours of dissolution in 0.1N HCl buffer and 87.67 ± 0.19, 95.08 ± 0.41, 93.01 ± 0.41 at the end of 12 hours of dissolution in 6.8 pH buffer. The formulas failed to follow compendial requirements of enteric coating tablet i.e., less than 10 % at the end of 2 hours of dissolution in 0.1N HCl buffer.

***In-Vitro* Drug Release Studies of Duloxetine Hydrochloride Enteric Coated Matrix Tablets Prepared by Using 5 % Coating Polymer with 10% Coating Layer of Cap:** The cumulative percent drug release for F4, F5, F6, was at the end of 2hrs of dissolution in 0.1N HCl buffer was found to be 8.51 ± 0.16, 8.70 ± 0.33, 8.51 ± 0.60. The formula F4, F5, F6 showed less than 10 % of drug release at the end of 2 hours of dissolution in 0.1N HCl buffer and 80.67 ± 0.82, 91.08 ± 1.22, 87.01 ± 1.64 at the end of 12 hours of dissolution in 6.8 pH buffer. The formulas followed compendial requirements of enteric coating tablet i.e., less than 10 % at the end of 2 hours of dissolution in 0.1N HCl buffer.

The cumulative percent drug release for F7, F8, F9, was at the end of 2hrs of dissolution in 0.1N HCl buffer was found to be 9.47 ± 0.29, 8.99 ± 0.72, 9.34 ± 0.33. The formula F7, F8, F9, showed less than 10 % of drug release at the end of 2 hours of dissolution in 0.1N HCl buffer and 90.60 ± 0.69, 95.44 ± 0.21, 92.92 ± 0.11 at the end of 12 hours of dissolution in 6.8 pH buffer. The formulas followed compendial requirements of enteric coating tablet i.e., less than 10 % at the end of 2 hours of dissolution in 0.1N HCl buffer.

***In-Vitro* Drug Release Studies of Duloxetine Hydrochloride Enteric Coated Matrix Tablets Prepared by using 5 % Coating Polymer with 20% Coating Layer of CAP:** The cumulative percent drug release for F10, F11, F12, was at the end of 2hrs of dissolution in 0.1N HCl buffer was found to be 6.40 ± 0.44, 6.50 ± 0.44, 6.79 ± 0.3. The formula F10, F11, F12 showed less than 10 % of drug release at the end of 2 hours of dissolution in 0.1N HCl buffer and 74.68 ± 0.06, 82.85 ± 0.38, 78.76 ± 0.26 at the end of 12 hours of dissolution in 6.8 pH buffer. The formulas followed compendial requirements of enteric coating tablet i.e., less than 10 % at the end of 2 hours of dissolution in 0.1N HCl buffer.

The cumulative percent drug release for F13, F14, F15, was at the end of 2hrs of dissolution in 0.1N HCl buffer was found to be 6.98 ± 0.44, 7.45 ± 0.58, 7.07 ± 0.16. The formula F13, F14, F15, showed less than 10 % of drug release at the end of 2hours of dissolution in 0.1N HCl buffer and 83.68 ± 0.45, 90.86 ± 1.16, 85.66 ± 0.34 at the end of 12 hours of dissolution in 6.8 pH buffer. The formulas followed compendial requirements of enteric coating tablet i.e., less than 10 % at the end of 2 hours of dissolution in 0.1N HCl buffer.

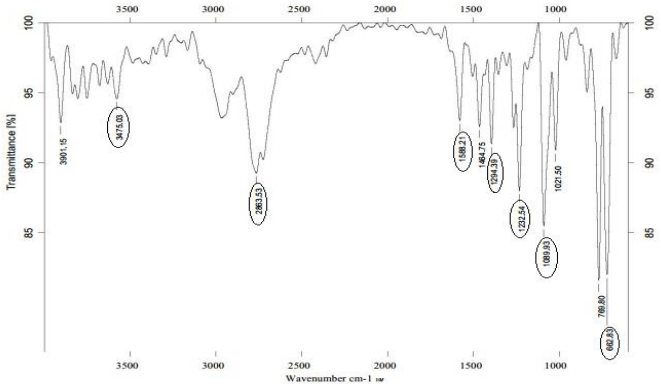

Figure.1.FTIR spectrum of Duloxetine HCl Drug

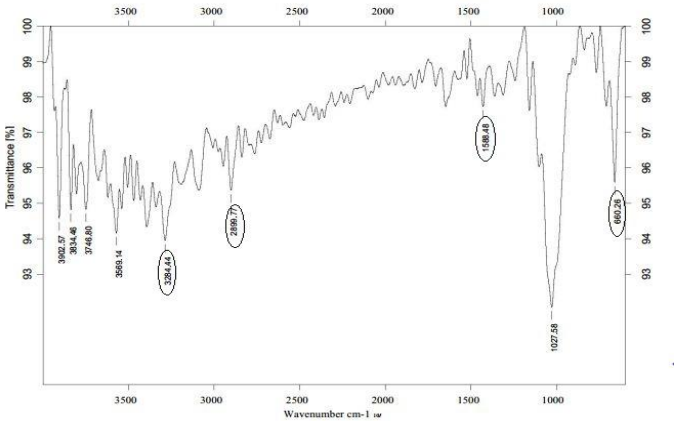

Figure.2.FTIR spectrum of Duloxetine HCl formulation

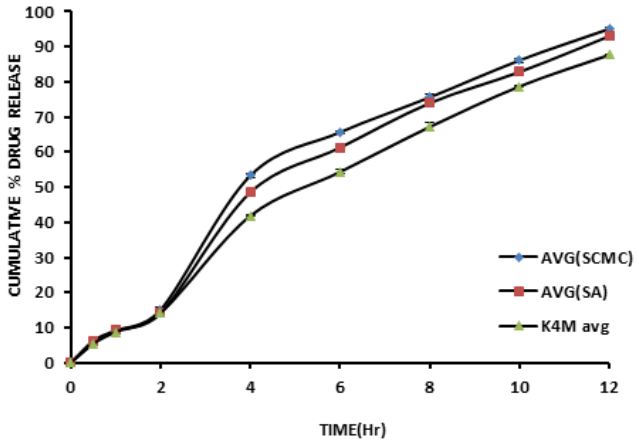

Figure.3.Comparative *In-vitro* dissolution profiles of Duloxetine HCl sustained release enteric coated tablets prepared with 5% enteric coating layer at 1:1 Drug: polymer ratio (F1, F2 and F3)

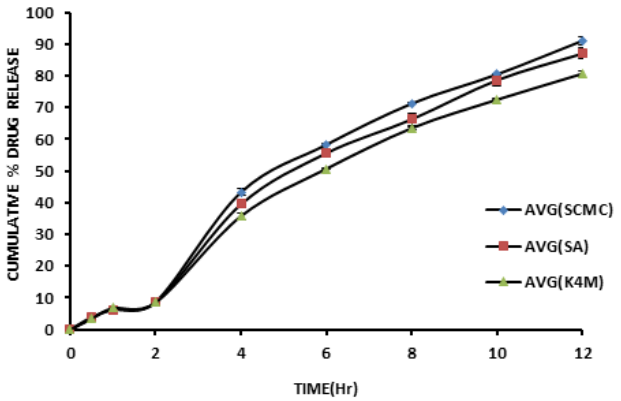

Figure.3.Comparative *In-vitro* dissolution profiles of Duloxetine HCl sustained release enteric coated tablets prepared with 10% enteric coating layer at 1:1 Drug: polymer ratio (F4, F5 and F6)

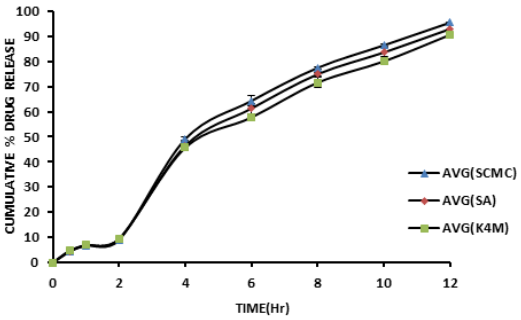

Figure.4.Comparative *In-vitro* dissolution profiles of Duloxetine HCl sustained release enteric coated tablets prepared with 10% enteric coating layer at 1:0.75 Drug: polymer ratio(F7, F8 and F9)

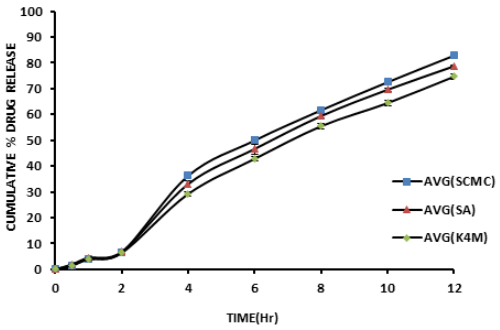

Figure.5.Comparative *In-vitro* dissolution profiles of Duloxetine HCl sustained release enteric coated tablets prepared with 20% enteric coating layer at 1:1 Drug:polymer ratio (F10, F11 and F12)

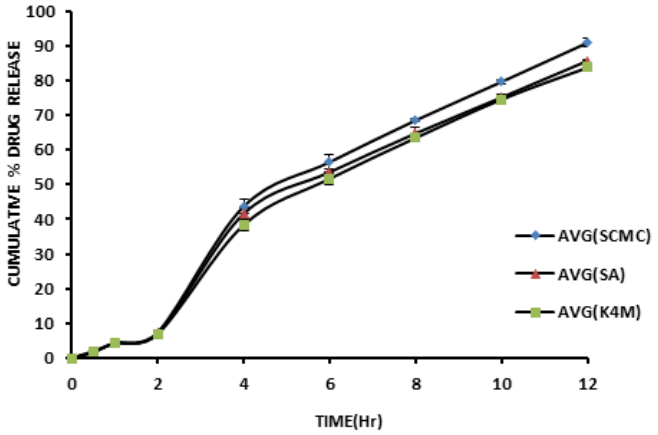

Figure.6.Comparative *In-vitro* dissolution profiles of Duloxetine HCl sustained release enteric coated tablets prepared with 20% enteric coating layer at 1:0.75 Drug: polymer ratio (F13, F14 and F15)

Table.2.Kinetic data for Duloxetine HCl formulations

Formulation	Zero Order Release		First Order Release		Higuchi Equation		Hixson-Crowell Equation		Korsmeyer-Peppas Equation	
	K_0	R^2	K_1	R^2	K_H	R^2	K_{HC}	R^2	N-Value	R_2
F1	7.606	0.979	0.066	0.987	27.860	0.957	0.125	0.994	1.041	0.976
F2	8.363	0.951	0.098	0.965	31.010	0.953	0.159	0.990	1.106	0.960
F3	8.113	0.963	0.089	0.966	29.920	0.954	0.149	0.991	1.087	0.961
F4	7.213	0.975	0.057	0.988	26.24	0.941	0.113	0.994	1.195	0.942
F5	8.137	0.968	0.082	0.969	29.69	0.939	0.143	0.99	1.288	0.938
F6	7.785	0.973	0.072	0.980	28.32	0.938	0.13	0.992	1.271	0.944
F7	8.031	0.964	0.081	0.972	29.4	0.941	0.14	0.989	1.246	0.937
F8	8.643	0.955	0.103	0.956	31.71	0.937	0.166	0.989	1.319	0.931
F9	8.357	0.96	0.091	0.97	30.62	0.931	0.152	0.991	1.282	0.939
F10	6.643	0.986	0.049	0.987	23.9	0.93	0.097	0.993	1.332	0.968
F11	7.431	0.977	0.062	0.981	26.89	0.932	0.117	0.991	1.369	0.952
F12	7.061	0.981	0.056	0.987	25.5	0.933	0.107	0.993	1.305	0.959
F13	7.546	0.973	0.065	0.984	27.39	0.934	0.12	0.992	1.287	0.95
F14	8.091	0.965	0.078	0.973	29.47	0.933	0.138	0.989	1.315	0.945
F15	7.677	0.966	0.068	0.979	27.95	0.933	0.125	0.989	1.306	0.945

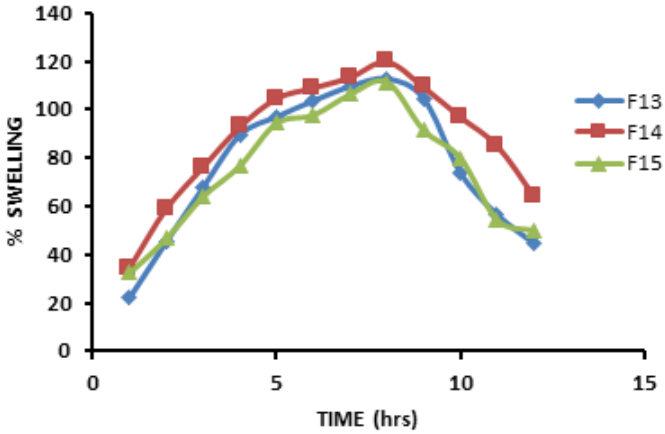

Figure.7. Swelling behaviour of matrix Formulations (F13, F14 and F15)

CONCLUSIONS

Hence in the present investigation enteric coated Sustained Release formulations of Duloxetine hydrochloride were prepared and evaluated by using hydrophilic polymers like HPMC K4M, Sodium carboxy methyl cellulose, Sodium alginate. Formulations prepared by using direct compression method showed sustained and the release up to 12 hours in the ratio of 1:1 and 1:0.75 with 20% coating layer. And they were formulated as F10-F15.therefore it was concluded that formulations containing 20% coating layer showed more sustained release and it is stable in both 1.2 pH buffer.

REFERENCES

Barnabas Wilson, Sustained release enteric coated tablets of pantoprazole: Formulation, in vitro and in vivo evaluation, 63, 2013, 131-140.

Chandan Garg, Once-daily sustained-release matrix tablets of metformin hydrochloride based on an enteric polymer and chitosan, J Pharm Educ Res, 4(1), 2013, 92-97.

Devraj, Studies on enteric coated sustained timed-release tablets of Metronidazole, journal of chemical and pharmaceutical research, 2(2), 2010, 226-232.

P.Rajesh, Enteric release formulation of acid-liable drug Duloxetine hydrochloride, Journal of Chemical and Pharmaceutical Sciences, 2(1), 2013, 62-65.

Pallavi Yerramsetty, Formulation, Development and Evaluation of delayed release tablets of Duloxetine Hydrochloride made of different Enteric Polymers, International Journal of Drug Development & Research, 4(1), 2012, 117-129.

Preethi mylavarapu, Formulation and evaluation of Duloxetine hydrochloride Delayed release enteric coated tablets, International Journal of Pharma and Bio Sciences, 2(3), 2011, 152-172.

Raja Subburayalu, Effect of pH of enteric polymer on dissolution profile of Duloxetine HCl delayed release pellets at various pH ranges, International Journal of Pharmaceutical Sciences and Research, 4(9), 2013, 3400-3407.

Rupesh S. Kamble, Formulation and development of enteric coated dosage form using ketorolac tromethamine, International Journal of Pharma. Research & development, 2(8), 2010, 126-135.

Saad M. Majeed, Formulation and evaluation of bilayer matrix tablets of Amoxicillin and Esomeprazole as an oral modified release dosage form for treatment of peptic ulcer, International Journal of Pharmacy and Pharmaceutical Sciences, 6(4), 2014, 134-142.

Singh Roobi**,** An overview on sustained release enteric coated tablet of pantoprazole, Journal of Drug Delivery & Therapeutics, 4(4), 2014, 130-136.

Surya Bhan Singh Rathore, Formulation and evaluation of enteric coated tablet of Duloxetine HCl azole, International Current Pharmaceutical Journal, 2013, 2(7), 2013, 126-130.

Vaishali Thakkar, Design and evaluation of a sustained release enteric coated dosage form of Fluoxetine HCl, Indian Journal of Pharmaceutical Education and Research, 46(4), 2012, 330-339.