RELEASE MODULATED DELIVERY OF DIGESTIVE ENZYME SUPPLEMENT

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ABSTRACT

A combination of proteolytic enzyme pepsin with amylolytic α- amylase serves as an ideal digestive enzyme supplement for the treatment of functional dyspepsia and exocrine pancreatic insufficiency. In the present research work, an attempt was made to develop a release modulated formulation which ensures the enteric delivery of acid liable α- amylase and stomach-specific delivery of pepsin using inlay tablet technology. Eight formulations of inner core layer containing α- amylase (fungal diastase) i.e., F1 to F8, were developed using varying ratios of microcrystalline cellulose and mannitol. The best suit formulation of inner core tablet was chosen and subjected to enteric coating using coating solutions C1 to C6 and evaluated for intactness of enteric coat. The formulations containing pepsin for immediate release outer coat i.e., P1 to P4, were formulated using mannitol, dicalcium phosphate, lactose and calcium carbonate, respectively, and evaluated for pharmaceutical parameters. The inlay tablet was formulated by coating best fit outer coat formulation on enteric coated inner core tablet using compression coating technique. The results of *in vitro* evaluation studies for formulated inlay tablet revealed that the prepared formulation releases pepsin in stomach, immediately followed by the release of α- amylase in alkaline environment of intestine.

Keywords: Pepsin, α- amylase (fungal diastase), release modulated drug release, inlay tablet

INTRODUCTION

Functional dyspepsia and exocrine pancreatic insufficiency are major contributors to impaired digestion along with abdominal discomfort. Oral administration of proteolytic enzyme pepsin with amylolytic enzyme α- amylase can be considered as an ideal physiological approach and has been found to be superior to acid suppression therapy, prokinetic agents, *Helicobacter-pyroli* eradication and placebo treatment for the condition of functional dyspepsia and exocrine pancreatic insufficiency[1-5]. But α- amylase is an acid sensitive enzyme that is highly prone to denaturation in the acidic environment of stomach, while pepsin remains stable and active in the acidic environment of stomach[6]. The instability of enzyme creates a need to develop enzyme delivery system that can protect α- amylase from the harsh acidic environment of the stomach without affecting the activity and stability of pepsin.

Vyas SP et al, employed Eudragit RS-100 as an enteric polymer for stabilization of fungal diastase in acidic environment of stomach by developing enteric spherules[7]. Dangre P et al, formulated Eudragit L-100 coated alginate beads loaded with α- amylase[8]. Compression coating could be a method of choice for enteric delivery of acid liable therapeutics such as tablets of bacteriophage[9]. Similar results were reported for tablets of ceftriaxone, coated with shellac and glycerol tri-stearate using direct compression method[10].

In the present research work, an attempt was made to develop an inlay tablet for gastro-protective delivery of α- amylase with pepsin which could impart a good degree of stability to these enzymes in harsh environment of the gastrointestinal tract.

MATERIALS

Pepsin and α-amylase were supplied as gift samples by Geno Pharmaceuticals, Goa and Unichem Labs Pvt Ltd., Goa. Eudragit L- 100 was procured from Evonik Industries, Mumbai. Cellulose acetate phthalate, Crospovidone, Croscarmellose, mannitol, microcrystalline cellulose, albumin and TCA (tricholroacetic acid) were procured from S.D. Fine Chemicals Ltd., Mumbai. DNS (di nitro salicylic acid) was procured from Molychem Labs.

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METHODOLOGY

Preformulation studies

Received samples of pepsin and α-amylase were subjected to physical characterization, solubility analysis in various physiological solvents, FTIR spectral analysis and for enzymatic activity-based UV Visible spectroscopy to confirm their identity and activity. Drug-excipient compatibility studies were carried out using FTIR spectroscopy[11-17].

Enzymatic activity-based UV visible spectroscopic method for analysis of pepsin

10 µg mL^{-1} solution of pepsin in hydrochloric acid buffer pH 1.2 was prepared by serial dilution method. 1 mL of this solution was added to 2 mL of albumin solution (2.5% w/V) and 1 mL of 0.3 M HCl and was kept aside for 10 minutes at room temperature. 3 mL of 5 % trichloroacetic acid solution was added to stop the action of pepsin on albumin. The resultant mixture was centrifuged using Electrocraft centrifuge at 1000 rpm for 10 minutes. The supernatant was analyzed using UV-visible spectrophotometer and its λ_{max} was determined. The same method was used for further analytical procedures related to pepsin[11,14,15].

Enzymatic activity-based UV visible spectroscopic method for analysis of α-amylase

10 µg mL^{-1} solution of α-amylase in phosphate buffer pH 7.4 was prepared by serial dilution method. 1 mL of this solution was added to 1 mL of 2 % starch solution and was incubated for 10 minutes. 2 mL of di-nitro salicylic acid (DNS) reagent was added to stop the reaction. 6 mL of distilled water was added to make up the volume to 10 mL. The resultant solution was analyzed UV-visible spectrophotometer and λ_{max} was determined. The same method was used for further analytical studies related to α-amylase[12,16,17].

Formulation design and development

Inlay tablets of pepsin and α-amylase were prepared in four different steps

Step I: Preparation of inner core tablet of α –amylase

Step II: Enteric coating of inner core tablet

Step III: Selection of formulation blend for immediate release layer of pepsin

Table I: Formulations for inner core tablets of α-amylase

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)
α –amylase	50	50	50	50	50	50	50	50
Croscarmellose sodium	2.1	2.1	2.8	2.8	-	-	-	-
Crospovidone	-	-	-	-	2.1	2.1	2.8	2.8
Mannitol	-	7.2	-	7.2	-	7.2	-	7.2
MCC	14.4	7.2	14.4	7.2	14.4	7.2	14.4	7.2
Talc	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
Magnesium stearate	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4

Table II: Formulations for enteric coating of tablets

Ingredient	C1	C2	C3	C4	C5	C6
Inner core tablet	70 mg	70 mg	70 mg	70 mg	70 mg	70 mg
Eudragit L -100*	3 %	4 %	5 %	-	-	-
Cellulose acetate phthalate	-	-	-	3 %	4 %	5 %
Triethyl citrate #	10 %	10 %	10 %	10 %	10 %	10 %
Acetone : water system (20:80)	100 mL	100 mL	100 mL	100 mL	100 mL	100 mL

** 3 % w/V of eudragit in acetone water system (80:20) solvent*

#10 % Weight of triethyl citrate equals to 10 % weight of enteric coated polymer

Step IV: Inlay tablet: Compression coating of pepsin layer on enteric coated inner core tablet.

Step I: Preparation of inner core tablet of α –amylase

Various formulation blends of inner core tablets containing α –amylase were prepared as per Table I and evaluated for precompression parameters. The prepared blends were compressed on multi-station tablet compression machine with 5 mm tooling using direct compression method. The tablets were evaluated for various pharmaceutical parameters and the best fit formulation among the eight formulations was selected for enteric coating[18-21].

Step II: Enteric coating of inner core tablet

Best fit formulation for the inner core tablet selected from step I was coated with various concentrations of enteric coated polymeric solutions as mentioned in Table II, using dip coating technique, and were subjected for further evaluation[22-24].

Step III: Selection of formulation blend for immediate release layer of pepsin

Formulation blends for immediate release pepsin were prepared as per Table III and evaluated for various precompression parameters. The prepared blends were compressed on tablet compression machine using 9 mm tablet tooling and subjected for evaluation of post compression parameters. Based on the results obtained, the best fit formulation was chosen for development of inlay tablet. The prepared formulations were subjected for various evaluation tests. Based on the evaluation tests, best fit formulation was chosen[18-21,25].

Table III: Formulation table immediate layer containing pepsin

Ingredient	P1 (mg)	P2 (mg)	P3 (mg)	P4 (mg)
Pepsin	10	10	10	10
Croscarmellose	6	6	6	6
Mannitol	128	-	-	-
Di calcium phosphate	-	128	-	-
Lactose	-	-	128	-
Calcium carbonate	-	-	-	128
Magnesium stearate	3	3	3	3
Talc	3	3	3	3

Step IV: Inlay tablet: Compression coating of pepsin layer on enteric coated inner core tablet.

Inlay tablet containing α-amylase and pepsin were prepared by compression coating technique using tablet compression machine. Best fit formulation for inner core tablet containing α-amylase was compressed using 5 mm tablet tooling and was coated with enteric coated polymer formulation selected in step II using dip coating technique. On the enteric coated inner core tablet, a coat of immediate release pepsin layer was applied by compression coating using 9 mm tabet tooling. The prepared tablets were evaluated for various pharmaceutical parameters[26-31].

RESULTS AND DISCUSSION

Preformulation studies

The results of evaluation of physical properties of pepsin and α-amylase showed that the received sample of enzymes complied with the standards. Enzyme activity-based UV visible spectroscopy confirmed the identity and activity of the received sample of enzymes. The results of compatibility studies carried out using FTIR spectroscopy confirmed the compatibility of enzymes and excipients.

Step I: Evaluation of inner core tablet of α –amylase

Precompression parameters

All the formulation blends for inner core tablet of α-amylase were evaluated for precompression parameters such as bulk density, tap density, flow property and compressibility. The results obtained confirmed that use of talc and magnesium stearate improves the flow property and compressibility of the formulation blend. The results of precompression parameters are summarized in Table IV.

Post compression parameters

All the prepared formulations complied with pharmacopeial specifications for weight variation test and drug content. Results of *in vitro* drug release studies in phosphate buffer pH 6.8 for first 2 h showed that formulation F3 containing 4 % of Croscarmellose sodium along with micro crystalline cellulose releases more than 80 % the α-amylase within 120 minutes. Hence, formulation F3 was selected for enteric coating. The results are tabulated in Table V. The *in vitro* release profile of α-amylase in phosphate buffer pH 6.8 is represented graphically in Fig. 1.

Table IV: Precompression parameters of formulation blend of core tablet α –amylase

Formulation No. (n=3)	Angle of repose	Bulk density (g mL^{-1})	Tapped density (g mL^{-1})	Hausner's ratio	Carr's index (%)
F1	27.28 ±0.15	0.44±0.03	0.52±0.07	1.19±0.07	16.15±0.06
F2	27.3 ±0.08	0.43±0.01	0.54±0.03	1.21±0.07	17.64±0.03
F3	25.4±0.30	0.44±0.03	0.53±0.09	1.19±0.08	15.96±0.06
F4	26.80±0.04	0.55±0.01	0.53±0.09	1.19±0.11	16.00±0.05
F5	25.57±0.65	0.43±0.02	0.52±0.04	1.20±0.05	17.20±0.07
F6	26.42±0.05	0.43±0.01	0.53±0.08	1.19± 0.02	16.40±0.07
F7	27.46±0.40	0.56±0.01	0.54±0.04	1.17±0.09	15.20±0.03
F8	28.32±0.04	0.44±0.02	0.54±0.07	1.19±0.07	16.10±0.04

Table V: Post compression parameters inner core tablet of α-amylase

Formulation No.	Thickness (mm) (n = 3)	Diameter (mm) (n = 3)	Weight variation (mg) (n=3)	Drug content (%) (n=3)	% CDR at end of 120 minutes (n=6)
F1	3.86±0.04	5.24±0.05	69.98±0.08	98.51±0.29	78.88±0.05
F2	3.74±0.01	5.28±0.05	70±0.05	96.54±0.45	52.75±0.48
F3	3.77±0.02	5.32±0.01	70.05±0.03	99.77±0.09	83.82±0.04
F4	3.82±0.02	5.28±0.01	70.03±0.05	98.85±0.77	51.38±0.05
F5	3.81±0.02	5.30±0.05	69.94±0.06	97.51±0.45	54.35±0.04
F6	3.68±0.02	5.27±0.03	70.10±0.07	98.59±0.51	61.78±0.04
F7	3.72±0.01	5.25±0.06	70.01±0.07	97.54±0.16	76.34±0.03
F8	3.83±0.01	5.24±0.05	69.10±0.05	96.51±0.08	59.43±0.07

Step II: Evaluation of enteric coated inner core tablet of α-amylase

The study for intactness of enteric coat showed that the formulation C3 containing 5 % of Eudragit L-100 as enteric coating polymer remained intact for more than 120 minutes in acidic pH and dissolved immediately in phosphate buffer pH 6.8 to release α-amylase loaded in inner core tablet. The results are summarized in Table VI. The results of *in vitro* drug release studies

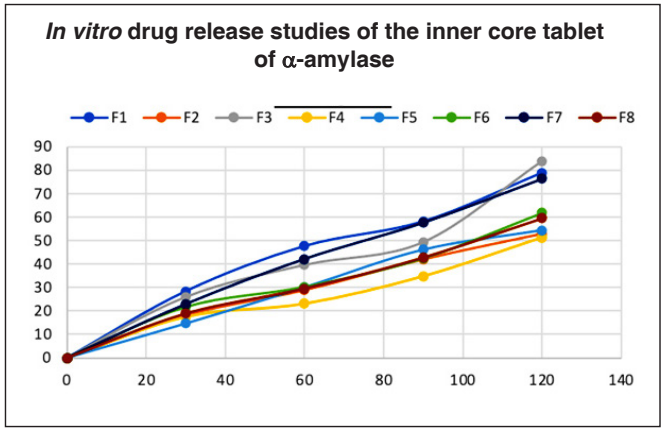

Fig. 1: *In vitro* drug release studies of the inner core tablet of α-amylase

Table VI: Evaluation intactness of enteric coated tablets

Formulation No.	Polymer used		Time for which the enteric coat was intact in acidic buffer pH 1.2
	Eudragit L-100	Cellulose acetate pthalate	
C1	3 %	-	25 minutes
C2	4 %	-	1 h 30 minutes
C3	5 %	-	2 h
C4	-	3 %	35 minutes
C5	-	4 %	1 h 28 minutes
C6	-	5 %	2 h

Table VII: Precompression parameters for immediate release layer of pepsin

Formulation No. (n=3)	Angle of repose	Bulk density (g mL^{-1})	Tapped density (g mL^{-1})	Hausner's ratio	Carr's index
P1	15.20±0.03	0.54±0.01	0.62±0.05	1.14±0.02	12.8±0.07
P2	13.00±0.18	0.55±0.03	0.64±0.04	1.15±0.20	13.00±0.06
P3	15.20±0.09	0.53±0.07	0.63±0.04	1.18±0.05	15.21±0.04
P4	13.98±0.10	0.54±0.05	0.63±0.05	1.17±0.03	14.82±0.02

Table VIII: Post compression parameters for immediate release layer of pepsin

Formulation No.	Thickness (mm) (n = 3)	Diameter (mm) (n = 3)	Weight variation (n=3)	Drug content (n=3)	Disintegration time in seconds (n=6)
P1	2.78±0.01	9.74±0.05	149.2±0.01	98.56±0.06	20 ± 3
P2	2.72±0.06	9.72±0.03	148.5±0.04	88.56±0.45	60 ± 6
P3	2.74±0.05	9.75±0.07	149.4±0.02	94.55±0.09	40 ± 2
P4	2.70±0.05	9.74±0.07	145.8±0.04	90.65±0.12	52 ± 3

revealed that the formulation C3 releases more than 80 % of α-amylase in phosphate buffer pH 6.8 within 120 minutes.

Step III: Evaluation of formulation for immediate release layer of pepsin

The results of various precompression and post compression parameters for immediate release layer of pepsin are tabulated in Tables VII and VIII. Based on the results, it was found that the formulation P3 containing optimum, concentration of Croscarmellose sodium as a super-disintegrating agent along with lactose as a filler binder disintegrated within 60 seconds and also provided satisfactory hardness to the compression coat. Hence, formulation P3 was selected for compression coating of enteric coated inner core tablet.

Step IV: Evaluation of inlay tablet

Inlay tablet consisting of enteric coated inner core tablet of α-amylase and immediate release layer of pepsin was prepared by compression coating technique. The best fit formulation F3 containing α-amylase for the inner core tablet was coated with enteric coat of formulation C3 using dip coating. To the enteric coated inner core tablet, a coat of immediate release pepsin layer was applied by compression coating technique. The results of *in vitro* drug release studies showed that the prepared formulation released pepsin in acidic pH and α-amylase was released in an alkaline pH. The results of *in vitro* drug release study are summarized in Table IX and graphically presented in Fig. 2.

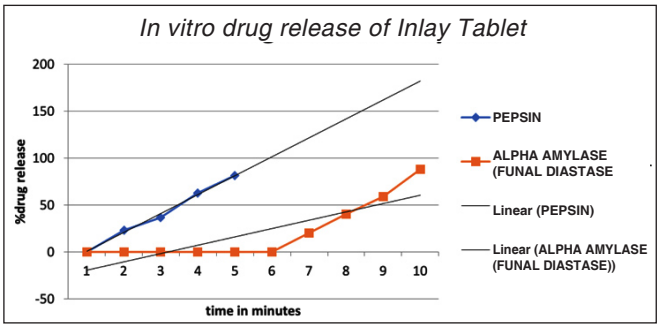

Fig. 2: *In vitro* drug release study of inlay tablet

Table IX: *In vitro* dissolution study of inlay tablet

Time in minutes	Cumalative % drug release of pepsin	Cumalative % drug release of α-amylase
0	0	0
30	23.40	0
60	36.18	0
90	62.98	0
120	81.26	0
150	-	19.94
180	-	40.12
210	-	58.85
240	-	87.97

CONCLUSION

Release modulated inlay tablet containing pepsin and α-amylase was developed which releases pepsin

immediately in the stomach while ensuring enteric delivery of acid labile α-amylase. Amylolytic enzyme α-amylase was incorporated in the inner core of the tablet and coated with enteric polymer using dip coating technique. Immediate release outer coat containing pepsin was given on enteric coated inner core tablet using compression coating technique.

Inner core tablets of α-amylase were formulated using different concentrations of release retardants and evaluated for various pharmaceutical parameters. The results of evaluation studies showed that the formulation F3 containing 14.4 mg of microcrystalline cellulose along with 4 % of Croscarmellose sodium gave more than 80 % *in vitro* drug release in 2 h in alkaline environment.

Inner core tablet containing α-amylase was coated using varying concentrations of Eudragit L-100 and cellulose acetate phthalate and were evaluated for intactness of enteric coat. The results showed that the formulation C3 containing 5 % of Eudragit L-100 can protect inner core tablet for more than 2 h in acidic environment of stomach. Varying concentrations of super-disintegrating agents were used to prepare the immediate release outer core of the tablet containing pepsin. The results of evaluation studies showed that the formulation P3 containing 4 % Croscarmellose sodium as super-disintegrating agent and mannitol as diluent disintegrated within 60 seconds and also gave the required hardness compared to other formulations.

Based on the evaluation studies, the selected formulations for the inner core tablet, enteric coat and immediate release outer coat were used to develop inlay tablet. The prepared tablet formulation was subjected for *in vitro* drug release study. It was found that the prepared formulation released pepsin in acidic environment of stomach, followed by release of α-amylase in alkaline environment of the intestine.

In conclusion, the inlay tablet can be regarded as a method of choice for delivery of acid-labile α-amylase in small intestine with stomach specific delivery of pepsin.

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