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Design and Development of Modified Release Solid Oral Dosage Form (Entacapone)

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A B S T R A C T

The present research work focuses on design and development of modified Release solid oral dosage form.entacapone: based on assessment of various parameters, in vitro drug dissolution profile and drug kinetics, hf14 was found to be optimized formulation.FT-IR & DSC studies revealed that there was no interaction between the drug and polymers used in the formulations. The drug release from hf14 was found to fit zero order of concentration independent and best fitted to higuchie model confirming to be diffusion assisted mechanism. Based on the mucoadhesive study, the optimized dosage form adhesive to gastro intestinal tract more than 12 hours. The marketed product released by first order kinetics by concentration dependent. In vivo bioavailability studies were conducted for optimized entacapone trilayer tablets and marketed product, the results were indicating that the optimized entacapone formulation was shown sustained release patterns where marketed product was shown immediate release

Keywords: Entacapone, modified drug release, trilayer

A R T I C L E I N F O

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1. Introduction

Requirement for the study: The need for the present investigation is to develop an Entacapone tablets and Tolcapone tablets controlled release formulation that releases the API release independent of its concentration. Entacapone marketed tablets found the release of drug in a controlled manner but the drug release is concentration dependent. Hence, the study was attempted with a plan to design Entacapone tri-layered matrix tablets and Tolcapone tri-layered matrix tablets by using Geo matrix technology that follows zero order kinetics i.e. Release of drug is independent of its concentration.

2. Materials and Methods

Materials: Entacapone, HPMC K 4 M, HPMC K 15 M, HPMC K 100 M, Xanthan gum, Ethyl cellulose, Eudragit L100 – 55, Carnauba wax, Sodium carboxyl methyl cellulose, Magnesium stearate, Talc.Dibasic calcium phosphate

Experimental Work: Compatibility studies between Drug and formulation exciepients. The study was to evaluate the compatibility of drug with polymers and others excipients and the study was reported by Differential Scanning Calroimetry (DSC) and Fourier Transform infrared (FTIR).

Micromeritic Studies:

Micromeritic Studies like Angle of repose, Carr's compressibility Index, Bulk dentistry, & Tapped density were studied.

Formulation of trilayer matrix tablets

Method of preparation

- Preparation of hydrophilic blend of polymers with drug for the matrix formulation.
- Preparation of hydrophobic blend for layering.
- Compression of hydrophobic layers on both sides of the matrix tablet.

The trilayered matrix tablets were prepared by direct compression method. The first step in the formulation was to develop the middle drug layer so as to give at least 90%drug release during 12 hours. This layer would be sandwiched between barrier layers so as to continue the drug release for 24 hours. The sandwich layer is hydrophobic layer. Formulation development of Entacapone trilayer matrix tablets

Formulation trails for active layer

Sixteen formulations (F1-F16) for active layer were formulated utilizing various concentrations and combinations of release retardant polymers HPMC (HPMC K4M, HPMC K15M & HPMC K100M), xanthan gum and sodium carboxy methyl cellulose.

Manufacturing procedure for active layer of Entacapone matrix tablets

Sifting & mixing: Accurately weigh required amount of entacapone and dibasic calcium phosphate and sift through #40 and mix for 15 minutes.

Accurately weigh required amount release retardant polymers of HPMC, Xanthan gum, sodium carboxy methylcellulose and ethyl cellulose and co- sift through #40 and mix for 10 minutes to above blend.

Lubrication: Accurately weigh required amount of magnesium stearate and sift through #60 and mix 5 minutes to above blend.

Compression: Compress the lubricated blend utilizing 12 mm round flat punches.

Preparation of barrier layer

Eight formulations (A - H) for barrier layer were formulated utilizing various concentrations and combinations of polymers carnauba wax, xanthan gum and ethyl cellulose.

Swelling Index study:

Swelling experiment was conducted on the prepared tablets using USP dissolution apparatus II at rotational speed of 50 rpm. The medium used was 900 mL phosphate buffer pH 5.5 at 37°C for entacapone matrix tablets and phosphate buffer pH 7.4 used for tolcapone matrix tablets. The swelling study was done upto 10h. The tablets were removed using a small basket and swollen weight of each tablet was determined.

The percentage of swelling was calculated according to the formula:

Percentage of swelling = (S/R) X 100

Evaluation of post compression parameters of Matrix and Tri-Layered Tablets

Physical appearance: The control of general appearance of tablet includes estimation of number of properties, for example, tablet size, shape, shading, nearness or nonappearance of scent, taste, surface composition and consistency of any ID marks. Weight variation twenty randomly taken tablets were weighed together and the average weight was determined. Each tablet was then weighed individually and deviation from average weight was calculated.

Hardness test: Hardness of ten randomly picked tablets was determined using Monsanto hardness tester.

Friability

Take a sample of 6.5g of tablets for tablet weight is equal to or less than 650 mg or take 10 tablets weight for tablet weight is more than 650 mg. The Friabilator was operated for 4 min at a speed of 25 rpm. The tablets were removed from the Friabilator, de-dusted and reweighed. The percent loss in weight due to abrasion and impact was calculated as, %Friability= (Loss in weight/ Initial weight) X 100.

Tablet size and Thickness:

The thickness of tablet is measured by Vernier Callipers scale.

Drug content / Assay

Entacapone: 20 tablets were accurately weighed individually and powdered. 200 mg of equivalent powder was dissolved in phosphate buffer pH 5.5. Final volume was made up to 100ml with phosphate buffer pH 5.5 and filtered. Absorbance of this solution was determined in a UV spectrophotometer at 377 nm. Amount of Entacapone in tablets was calculated by using regression equation.

Tolcapone:

20 tablets were accurately weighed individually and powdered. 200 mg of equivalent powder was dissolved in phosphate buffer pH 7.4. Final volume was made up to 100ml with phosphate buffer pH 7.4 and filtered. Absorbance of this solution was determined in a UV spectrophotometer at 257 nm. Amount of Tolcapone in tablets was calculated by using regression equation.

***In-vitro* drug release determination:** This involved study of release profile of the prepared tablets using the following table

Drug release models:

Drug release mechanisms and kinetics are the two important characteristics of a drug delivery system in describing drug dissolution profile. To describe the kinetics of the drug release from matrix tablet, mathematical models such as zero-order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models were used.

Stability studies:

The optimized formulation was stored in a stability chamber for stability studies (REMI make). Accelerated

Stability studies were carried out at 40 ^{0}C / 75 % RH & 25°c/60% RH for the best formulations for 6 months.

Mucoadhesive/Bioadhesive study

Measurement of mucoadhesive strength of tablets:

Bioadhesive strengths such as peel strengrh, tensile strength and shear strengths were quantified for trilayer tablets by utilizing freshly excised goat intestinal mucosa as substrates. The studies were performed within 3 hours of accretion of the mucosa. The mucosa obtained from abattoir anon after sacrifice was kept in Krebs buffer at 4°C. The underlying tissue was dissected out and the mucosa along with the adherent mucus was stored in isotonic phosphate buffer (pH 6.6) at 37°C for about 15 minutes afore the commencement of experiment.

In vitro residence time: In vitro residence time was tenacious utilizing a modified USP disintegration apparatus. The medium for disintegration apparatus is composed of 800 mL isotonic buffer (Phosphate buffer pH 6.6) maintained at 37°C. The tablet was pressed over the excised goat intestinal mucosa for 30 seconds that was secured to the surface of a glass slab and sanctioned for five minutes. The glass slab was vertically fine-tuned to the apparatus and sanctioned to move up and down so that the tablet was plenarily immersed in the buffer solution at the lowest point and was out at the apex. The time compulsory for consummate erosion or detachment of the tablet from the mucosal surface was recorded.

3. Results and Discussions

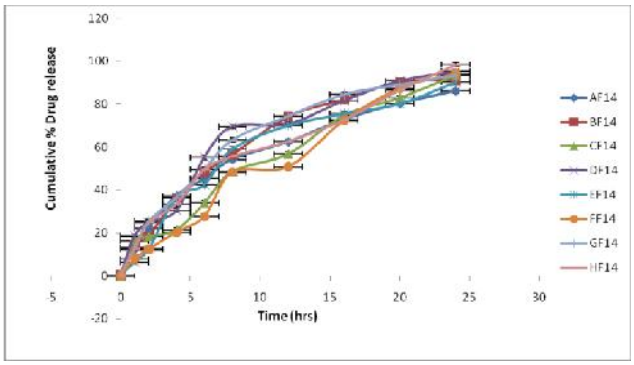

Figure 1: *In-vitro* dissolution profile of Entacapone trilayer tablets AF14-HF14

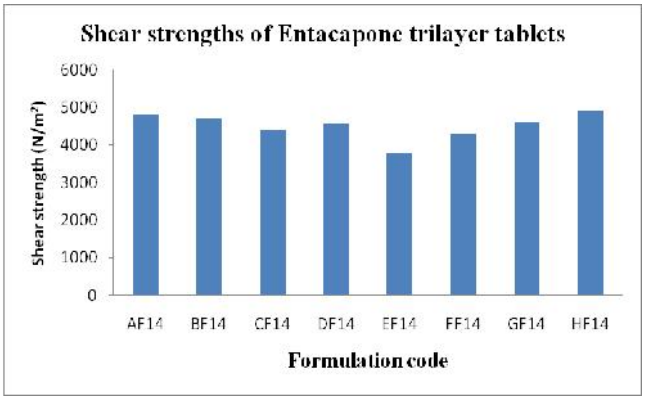

Figure 2: Shear strengths of Entacapone trilayer tablets

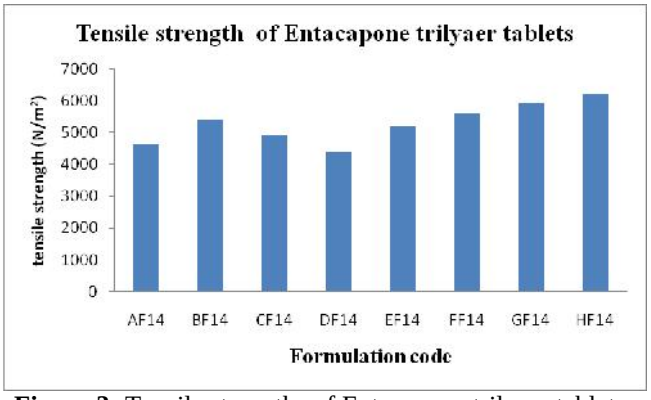

Figure 3: Tensile strengths of Entacapone trilayer tablets

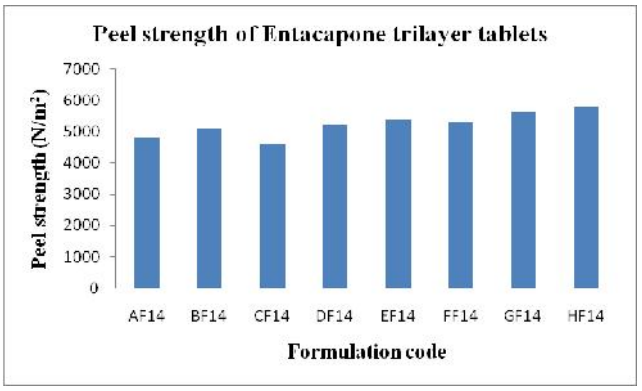

Figure 4: Peel strengths of Entacapone trilayer tablets

Table 1A: Powder flow properties of Entacapone active layer blend (F1-F16) (n=3)

Powder properties	F1	F2	F3	F4
Bulk density (g/cc)	0.556±0.02	0.536±0.08	0.500±0.02	0.517±0.09
Tapped density(g/cc)	0.625±0.08	0.577±0.03	0.556±0.08	0.577±0.01
Angle of repose (°)	31.42±0.42	30.85±0.52	32.18±0.42	29.45±0.48
Carr's index	11.11±0.89	7.14±0.62	10.00±0.51	10.34±0.86
Hausner's ratio	1.13±0.08	1.05±0.06	1.11±0.06	1.12±0.05

Table 1B: Powder flow properties of Entacapone active layer blend (F1-F16)(n=3)

Powder properties	F5	F6	F7	F8
Bulk density (g/cc)	0.484±0.06	0.469±0.08	0.484±0.02	0.577±0.09
Tapped density(g/cc)	0.517±0.03	0.536±0.12	0.556±0.04	0.625±0.12
Angle of repose (°)	28.62±0.85	31.06±0.17	28.18±0.22	27.45±0.46
Carr's index	6.45±0.15	12.50±0.50	12.90±0.18	7.69±0.12
Hausner's ratio	1.07±0.03	1.14±0.04	1.15±0.07	1.08±0.04

Table 1C: Powder flow properties of Entacapone active layer blend (F1-F16)(n=3)

Powder properties	F9	F10	F11	F12
Bulk density (g/cc)	0.444±0.05	0.517±0.06	0.469±0.08	0.536±0.06
Tapped density(g/cc)	0.480±0.04	0.600±0.04	0.536±0.06	0.577±0.05
Angle of repose (°)	28.65±0.68	27.56±0.46	29.65±0.58	26.45±0.32
Carr's index	7.41±0.98	13.79±0.85	12.50±0.58	7.14±0.85
Hausner's ratio	1.08±0.05	1.14±0.04	1.14±0.06	1.08±0.03

Table 2: Powder flow properties of Entacapone barrier layer blend (AF14-HF16) (n=3)

Powder properties	AF14	BF14	CF14	DF14
Bulk density (g/cc)	0.715±0.04	0.712±0.06	0.512±0.02	0.705±0.04
Tapped density(g/cc)	0.787±0.10	0.790±0.09	0.629±0.07	0.767±0.02
Angle of repose (°)	33.69±0.63	34.93±0.66	33.12±0.63	31.89±0.43
Carr's index	9.14±0.91	9.87±0.93	18.6±0.51	8.08±0.91
Hausner's ratio	1.10±0.02	1.15±0.02	1.17±0.02	1.08±0.04

Table 2B: Powder flow properties of Entacapone barrier layer blend (AF14-HF16) (n=3)

Powder properties	AF14	BF14	CF14	DF14
Bulk density (g/cc)	0.715±0.04	0.712±0.06	0.512±0.02	0.705±0.04
Tapped density(g/cc)	0.787±0.10	0.790±0.09	0.629±0.07	0.767±0.02
Angle of repose (°)	33.69±0.63	34.93±0.66	33.12±0.63	31.89±0.43
Carr's index	9.14±0.91	9.87±0.93	18.6±0.51	8.08±0.91
Hausner's ratio	1.10±0.02	1.15±0.02	1.17±0.02	1.08±0.04

Table 3: Physical and chemical evaluation of EntacaponeTrilayer tablets (AF14-HF14)

TESTS	AF14	BF14	CF14	DF14	EF14	FF14	GF14	HF14
Physical appearance								
Color	Pale yellow	Pale yellow	Pale yellow	Pale yellow	Pale yellow	Pale yellow	Pale yellow	Pale yellow
shape	Round	Round	Round	Round	Round	Round	Round	Round
Hardness(Kg/Cm^2)	7	6	6	7	6	7	6	**7**
Thickness (mm)	4.86±0.2	4.82±0.2	4.86±0.2	4.81±0.2	4.88±0.2	4.91±0.2	4.85±0.2	4.92±0.2
Weight variation (mg)	596±20	599±20	595±20	594±20	597±20	595±20	596±20	600±20
Friability (%)	0.15	0.28	0.26	0.30	0.35	0.18	0.23	0.24
Assay (%)	97.5	96.8	96.2	98.0	95.7	97.4	96	98.9
Swelling Index (%)	134.68	142.52	159.64	167.53	179.12	186.43	206.21	219.43
In vitro residence time, n=3	7 hr 30 min	8 hr 30 min	8 hr 15 min	7 hr 15 min	8 hr 45 min	9 hr 30 min	Above 12 hrs	Above 12 hrs

Table 4: *In-vitro* dissolution studies of Entacapone Trilayer tablets (AF14-HF14)

Time(h)	AF14	BF14	CF14	DF14	EF14	FF14	GF14	HF14
1	12.34±0.01	14.22±0.04	16.21±0.04	18.47±0.05	6.16±0.01	7.85±0.04	13.22±0.04	**12.49±0.04**
2	22.11±0.02	18.21±0.05	18.23±0.05	24.54±0.05	12.28±0.02	12.25±0.05	25.32±0.02	**24.52±0.04**
4	37.15±0.03	36.32±0.04	21.28±0.05	30.43±0.05	36.38±0.02	20.23±0.05	36.35±0.03	**33.35±0.03**
6	45.25±0.05	48.15±0.04	33.79±0.05	55.25±0.04	42.45±0.03	27.54±0.05	49.62±0.04	**49.53±0.05**
8	54.16±0.09	56.42±0.08	48.53±0.05	69.45±0.02	58.98±0.04	48.15±0.04	63.32±0.05	**55.54±0.07**
12	62.34±0.05	74.12±0.05	56.75±0.06	70.74±0.03	69.99±0.05	50.75±0.05	74.46±0.05	**62.59±0.05**
16	72.75±0.03	82.24±0.04	74.68±0.06	81.65±0.03	75.55±0.04	72.32±0.01	84.53±0.04	**72.63±0.05**
20	80.24±0.05	90.21±0.05	82.95±0.07	90.85±0.02	80.20±0.05	87.22±0.05	89.15±0.06	**86.53±0.06**
24	86.12±0.04	91.22±0.02	93.45±0.01	95.25±0.02	90.24±0.03	94.24±0.04	93.55±0.04	**98.29±0.09**

Table 5: Release order kinetics of Entacapone Trilayer tablets (AF14-HF14)

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Peppas R^2	Peppas n value
AF 14	0.929	0.815	0.931	0.782	0.590
BF 14	0.909	0.734	0.943	0.738	0.564

CF 14	0.941	0.739	0.922	0.736	0.565
DF 14	0.960	0.662	0.927	0.708	0.516
EF 14	0.927	0.701	0.930	0.693	0.518
FF 14	0.960	0.716	0.936	0.760	0.558
GF 14	0.954	0.750	0.971	0.756	0.557
HF 14	0.994	0.855	0.972	0.785	0.724

Table 6: In-Vitro dissolution profile of Marketed product

Time (min)	Cumulative % drug release
5	6.15±0.01
10	13.32±0.05
20	51.25±0.07
30	85.25±0.06
45	96.85±0.05
60	99.25±0.02

4. Conclusion

It was inferred that trilayer entacapone matrix tablets were effectively arranged by direct compression method with mucoadhesive property utilizing diverse polymers combination with patient compliance and consistence by lessening the dose recurrence in proficient administration of parkinson's illness.

Future Scope: We are planning to develop the trilayer matrix tablets with the combination of carbidopa, levodpoa and entacapone trilayer tablets to extend the drug release profile upto 24hrs and to lessening the patient compliance by lessening the dose recurrence in proficient administration of parkinson's illness.

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