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Design and evaluation of entacapone controlled release trilayer matrix tablets in the management of parkinson's disease

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ABSTRACT

The main objective of the present study was to prepare controlled release (CR) matrix tablets of Entacapone trilayer tablets to achieve zero-order drug release for sustained plasma concentration. Entacapone tablets were prepared by direct compression and consist of middle active layer with different grades of hydroxypropylmethylcellulose (HPMC), Guar gum, ethyl cellulose; upper and lower layers were prepared with Carnauba wax, Guar gum, sodium CMC and DCP. The tablets were also evaluated for physicochemical characteristics and release kinetics. The physicochemical characteristics of the prepared tablets were satisfactory. The developed drug delivery systems showed prolonged drug release rates over a period of 24 h. The release profile of the optimized formulation (HF14) was described by the Zero-order and Higuchi model. These results also demonstrated the suitability of three-layered tablet formulation of Entacapone to provide controlled release for prolonged period of time and improved linearity for Entacapone in comparison to marketed product with conventional drug release profile in the management of Parkinson's disease.

Keywords: Entacapone, Parkinson's disease, HPMC, Guar gum, Geomatrix.

INTRODUCTION

Controlled release pharmaceutical systems have been developed and studied to improve the performance of drugs and in particular to increase their pharmacological effect and reduce any side effects[1]. The basic characteristic of the systems is that the rate of drug absorption may be adjusted through a controlled rate of drug release from the dosage forms.

A number of design options are available to control or modulate drug release from a drug delivery system. Most oral controlled release dosage forms fall in the category of matrix, reservoir or multi-layer systems. Lately, multi-layer matrix systems are gaining importance in the design of oral sustained drug delivery systems. A multi-layer system consists, usually, of a hydrophilic matrix core containing the active ingredient and one or two impermeable or

semi-permeable polymeric coatings (barrier-layer) applied on one or both faces of the core during tabletting[2, 3, & 4]. The barrier layers delay the interaction of active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate[5,6]. In the device, the coat layers prevent the water penetration through the protected core for some duration. After this phase during the subsequent dissolution process, the swollen barriers erode and the surface available for drug release slowly increases. In this way the decrease of delivery rate due to the increase in diffusion path length is counter balanced by the simultaneous increase of the area available for drug release[7,8]. The use of naturally occurring biocompatible gums has been the focus of recent research activity in the design of dosage forms for oral controlled release administration, and hydrophilic polymers matrix systems are widely used because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance[9]. Guar gum (GG) is soluble in water, anionic hetero polysaccharide and to be sensitive to pH and ionic strengths. It swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug can slowly diffuse[10] and is used for the fabrication of matrices with uniform drug release characteristics[11&12].

Geomatrix technology

There have been different approaches to achieve zero-order drug release from dosage forms for sustained plasma concentration. Among different approaches to achieve zero-order release from hydrophilic matrix technologies, multilayer matrices have been widely evaluated and developed for commercial products under the trade name of Geomatrix. The technology makes use of bilayer or trilayer tablets to modulate the release and to achieve constant release[13]. Entacapone is a selective, reversible catechol-O-methyl transferase (COMT) inhibitor, used in the treatment of Parkinson's disease. It is a member of the class of nitrocatechols. The principal therapeutic action of the COMT inhibitors is to block this peripheral conversion of levodopa to 3-O-methyl DOPA, increasing both the plasma half-life of levodopa as well as the fraction of the dose that reaches the CNS[14]. The short half life of Entacapone necessitated for fabricating extended release matrix tablets to provide a therapeutic amount of drug and maintain the desired drug concentration i.e. the drug-delivery system should deliver drug at a rate dictated by the needs of the body over a specific period of time. Sustained release tablets are intended to take once or twice daily, when compared with conventional dosage forms that may have to take three or four times daily to achieve the same therapeutic effect. The objective of the present study was to develop a trilayered tablet of Entacapone with different hydrophobic and hydrophilic polymers. The results indicate that the optimized trilayered Entacapone tablet can be successfully used for treatment of Parkinson's disease.

MATERIALS AND METHODS
MATERIALS

Entacapone pure drug was generous gift from Aurobindo Pharma Limited, Hyderabad, India. Sodium carboxyl methyl cellulose, HPMC K 4 M, HPMC K 15 M & HPMC K 100 M were obtained from Rubicon labs, Mumbai. Guar gum and Carnauba wax were gifted from MSN Labs Ltd. Hyderabad. Entacapone (200mg) film coated tablets were purchased from Orion Pharma Ltd, Mumbai. All other chemicals used were of analytical grade.

METHODS

Pre-compression parameters

Angle of Repose

In powder frictional forces can be measured with the help of angle of repose. Angle of repose is the maximum angle which is possible between surface of pile of powder and horizontal plane i.e. height.

$\tan\Theta = h/r$

$\Theta = \tan^{-1} h/r$

Where Θ = Angle of repose

h= height of pile

r = radius of pile[15].

Carr's compressibility Index

The propensity of the powder to be compressed is measured by compressibility index and it also helps in measurement of settling property and inter particulate interaction.

Carr's index (%) = $\rho t - \rho o * 100 / \rho t$

Where ρt = Tapped density gram/ml

ρo = Bulk density gram/ml

Bulk dentistry

It is denoted by ρb and is defined as mass of powder divided by bulk volume (The United States Pharmacopeial Convention Stage 6 Harmonization Official December 1, 2012, 616.).

Tapped density

An increased in bulk density which is attained after mechanical tapping in measuring cylinder is called as tapped density.

Tapped density= Weight of powder taken/ Tapped Volume.

Hausner ratio

The propensity of the powder to be compressed is measured by Hausner ratio. Interparticulate interaction and settling property can be measured by Hausner ratio.

Hausner ratio= Tapped density/ Bulk density

Hausner ratio= Vo/Vf

Where, Vo= Unsettled apparent volume

Vf= Final tapped volume[16]

Formulation of controlled release Entacapone trilayer matrix tablets

The trilayered matrix tablets of Entacapone were prepared by direct compression method. The first step in the formulation was to develop the middle active layer so as to give at least 90%drug release during 12hours. The release profile of this layer might not be of constant rate type but would be preferably of constantly falling rate type. This layer would then be sandwiched between barrier layers (Upper & Lower layers) so as to continue the drug release for 24 h.

Preparation of middle active layer

Sixteen formulations (F1-F16) for active layer were prepared by direct compression method using polymers like different HPMC grades, Guar gum, Sodium CMC, EC. All the formulations were varied in concentration of polymers, talc (1.5mg) & magnesium stearate (1.5mg) constituted in all the formulations. These materials were screened through ≠60 and mixed together in motor by using pestle. Final mixtures were compressed by using 12mm.

Table 1: Formulation trails for middle active layer (F1-F16)

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Entacapone	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200
HPMC K 4M	50	55	60	---	---	----	25	30	----	----	----	----	----	----	----	----
HPMC K 15M	---	----	----	50	55	60	45	40	----	----	----	----	----	----	----	----
HPMC K 100M	---	---	---	----	---	----	----	----	40	45	50	55	60	62.5	65	67.5
Ethyl cellulose	22	30	32	22	30	32	15	15	40	35	22	30	32	22.5	22.5	22.5
Guar gum	20	22	25	20	22	25	30	32	15	17.5	20	22	25	30	30	30
Sodium carboxy methyl cellulose	25	15	10	25	15	10	15	15	27	21.5	25	15	10	12	10	12
Dibasic calcium phosphate	30	25	20	30	25	20	17	15	25	27	30	25	20	20	19.5	15

Diameter flat punches on a sixteen station rotary tablet press. Formulation of active layer was depicted in **Table 1**. The prepared tablets were subjected to dissolution studies.

Preparation of upper and lower layers

The barrier layers was formulated employing hydrophobic swellable polymer natural wax i.e. carnauba wax the swelling erosion modelling fillers which include water soluble DCP, EC and Guar gum. The procedure adopted to make the compacts was via direct compressions. For the first procedure the wax, Guar gum and the filler was mixed in mortar and lubricated with magnesium stearate. Formulation of upper and lower layers was depicted in **Table 2**.

Formulation of Entacapone tryilayer tablets

The powder mixtures required for active and barrier layers were weighed accurately and thoroughly mixed using mortor and pestle for about 20 minutes.

Initially, the volume of die cavity; (12mm, round) was adjusted equivalence to the weight of trilayered matrix tablets (600mg). Then the pre weighed amount of powder equivalent to bottom layer (125mg) was taken and placed in the die cavity and slightly compressed for uniform spreading. The upper punch was lifted up and the granules equivalent to 200mg of the drug was placed over the bottom layer in the die cavity and again slightly compressed. The remaining volume of the die cavity was filled with pre weighed (125mg) amount of powder equivalent to top layer and compressed with the full force of compression on rotary tablets press to obtain tri-layered tablets. Tri-layered matrix tablets of each composition were compressed and tested for their friability, Hardness, drug content and drug release characteristics with a suitable number of tablets for each test.

Table 2: Composition of Entacapone trilayer matrix tablet

INGREDIENTS	AF14	BF14	CF14	DF14	EF14	FF14	GF14	HF14
MIDDILE ACTIVE LAYAER (F14) (mg)								
Entacapone	200	200	200	200	200	200	200	200
HPMC K 100M	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
Ethyl cellulose	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5
Guar gum	30	30	30	30	30	30	30	30
Sodium CMC	12	12	12	12	12	12	12	12
Dibasic calcium phosphate	20	20	20	20	20	20	20	20
UPPER AND LOWER LAYER(mg)								
Carnauba wax	20	25	30	35	40	42.5	45	50
Guar gum	40	40	38	35	35	32.5	30	30
Ethyl cellulose	12	10	14	12	15	12	12	12
Dibasic calcium phosphate	50	47	40	40	32	35	35	30
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

EVALUATION OF TRILAYER MATRIX TABLETS OF ENTACAPONE

Hardness

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

Friability

A sample of twenty randomly selected tablets were accurately weighed and placed in a Roche Friabilator. 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.

Weight variation

The weight variation test was performed as per the USP. 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.

Drug content / Assay

Five tablets were weighed individually and powdered. Then the powder of tablet equivalent to 200mg was weighed and dissolved in phosphate buffer 6.8pH, the solution was filtered and diluted using phosphate buffer pH6.8 and then the drug content was analyzed using UV spectrophotometer at 377nm.

In-vitro drug release profile

In vitro drug release studies for developed trilayer matrix tablets were carried out by using dissolution apparatus II paddle type (Electrolab TDL-08L). The drug release profile was studied in 900ml Phosphate buffer pH 6.8 at 37± 0.5^0C temperature. The amount of drug release was determined by UV visible spectrophotometer (Shimadzu UV 1800) at 377nm.

Drug release kinetics

To describe the kinetics of the drug release from matrix tablet, mathematical models such as Zero-order, First order and Higuchi, models were used. The criterion for selecting the most appropriate model was chosen on the basis of the goodness-or fit test.

DRUG-EXCIPIENT COMPATIBILITY STUDIES

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The samples were dispersed in KBr and compressed into disc/pellet by application of pressure. The pellets were placed in the light path for recording the IR spectra. The scanning range was 400-4000 cm^{-1} and the resolution was 1 cm^{-1}.

RESULTS AND DISCUSSION

Pre-compression parameters

All the powder mixture belonging to different formulations was tested for micrometrics studies in order to determine the flow properties. All the formulations AF14 to HF14 showed good flow properties, the results are summarized in **Table 3.**

Table 3: Powder flow properties of Entacapone, powder blends of active layer and barrier layer polymers

Powder properties	AF14	BF14	CF14	DF14	EF14	FF14	GF14	HF14
Bulk density (g/cc)	0.7151±0.04	0.7121±0.46	0.512±0.02	0.7050±0.14	0.714±0.56	0.684±0.78	0.695±0.02	0.704±0.56
Tapped density (g/cc)	0.787±0.10	0.790±0.93	0.629±0.17	0.767±0.2	0.795±0.93	0.746±0.82	0.781±0.048	0.796±0.93
Angle of repose (o)	33.69±0.63	34.93±0.66	33.12±0.63	31.89±0.43	24.39±0.66	33.09±0.27	28.15±0.02	26.39±0.66
Carr's index	8.09±0.91	8.02±0.93	9.49±0.51	8.29±0.91	8.35±0.94	7.62±0.58	7.28±0.33	8.15±0.94

Preparation of middle active layer

The matrix tablets of Entacapone were prepared without the barrier layers. All the formulation trails were subjected to *in vitro* dissolution to determine the release profiles.

Table 4: Dissolution profile of different formulations Entacapone active layer (F1-F8)

TIME (h)	F1	F2	F3	F4	F5	F6	F7	F8
1	27.12± 0.04	27.56± 0.02	38.2± 0.01	19.12± 0.01	15.4± 0.01	25.4± 0.01	28.7± 0.01	10.3± 0.01
2	42.6± 0.01	39.12± 0.02	48.2± 0.04	39.2± 0.02	38.3± 0.02	35.2± 0.02	37.4± 0.02	25.1± 0.02
4	63.6± 0.02	42.7± 0.01	59.4± 0.02	55.12± 0.01	42.7± 0.02	47.6± 0.01	64.5± 0.04	35.3± 0.04
6	76.12± 0.01	57.2± 0.05	75.11± 0.01	64.4± 0.02	54.4± 0.01	60.4± 0.02	72.8± 0.04	55.9± 0.04
8	83.02± 0.04	75.11± 0.03	86.2± 0.04	72.1± 0.04	79.11± 0.04	65.3± 0.03	82.6± 0.02	68.3± 0.05

10	89.2± 0.05	89.12± 0.01	88.4± 0.03	79.3± 0.04	89.2± 0.02	72.7± 0.01	88.2± 0.01	69.6± 0.01
12	94.9± 0.01	95.2± 0.02	92.1± 0.02	89.6± 0.03	94.3± 0.01	86.9± 0.02	92.4± 0.01	70.8± 0.03

Table 5: Dissolution profile of different formulations Entacapone active layer (F9-F16)

TIME (h)	F9	F10	F11	F12	F13	F14	F15	F16
1	13.8±0.01	15.7±0.01	25.5±0.02	17.5±0.01	31.8±0.01	30.5±0.01	14.8±0.04	14.5±0.02
2	35.4±0.03	40.4±0.02	39.4±0.01	25.8±0.02	42.4±0.01	40.7±0.02	32.7±0.04	32.2±0.02
4	55.6±0.05	58.3±0.04	52.6±0.04	45.3±0.04	62.8±0.02	72.4±0.01	55.6±0.01	55.4±0.01
6	65.2±0.04	67.7±0.04	65.2±0.04	50.4±0.01	79.1±0.04	80.4±0.04	65.4±0.02	75.4±0.04
8	69.6±0.01	75.2±0.01	72.7±0.02	57.8±0.02	86.6±0.02	88.2±0.01	82.2±0.01	85.3±0.04
10	72.8±0.04	86.8±0.02	87.4±0.01	82.6±0.02	92.8±0.04	93.2±0.01	88.1±0.03	89.2±0.03
12	85.3±0.01	92.7±0.01	96.5±0.02	96.2±0.01	96.5±0.01	96.6±0.04	93.7±0.01	95.2±0.01

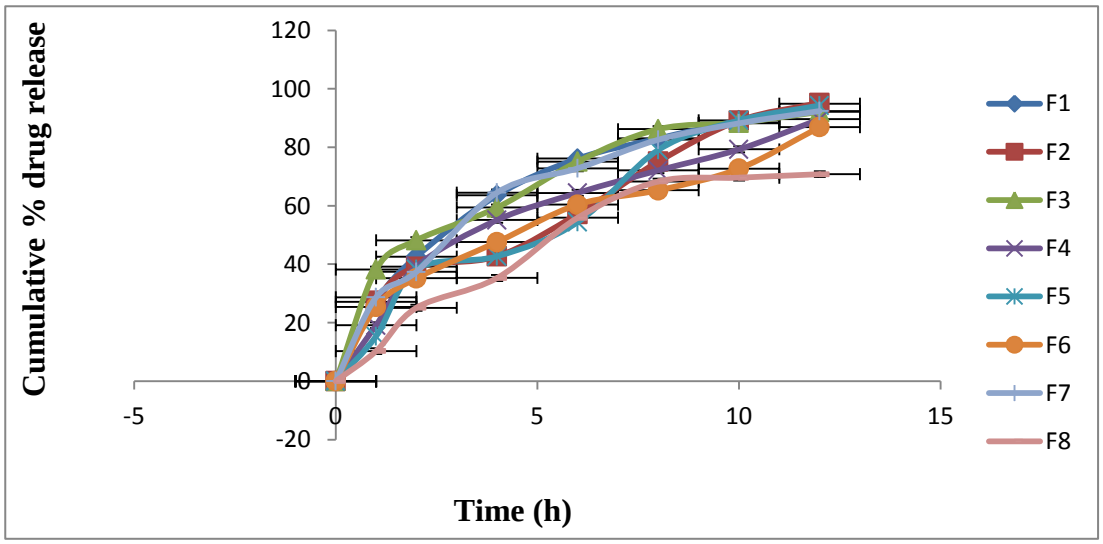

Figure 1*: In vitro* Dissolution profile of F1-F8 Entacapone active layer formulations

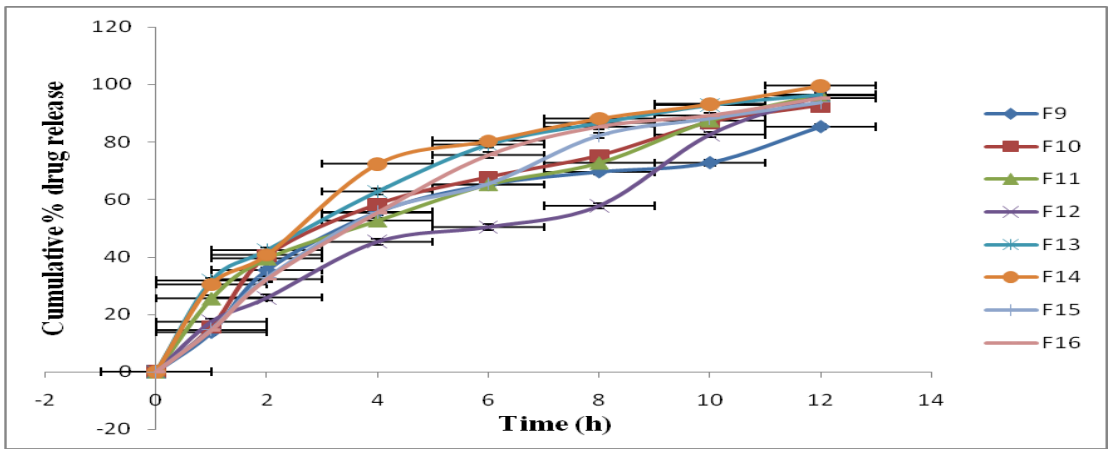

Figure 2: In vitro Dissolution profile of F9-F16 Entacapone active layer formulations

From the above results, among all the formulations the formulation F14 was decided as optimized formulation for active layer based on the highest drug release i.e. 96.6±0.04 within 12hrs when compared with other preparations (**Table 4&5; Figure 1 & 2**). Formulation F14 was choosen as active layer for further studies.

Evaluation of trilayer matrix tablets of Entacapone

Figure 3: Entacapone trilayer matrix tablets

The Entacapone trilayer matrix tablets are shown in **Figure 3**. Sustained release tablets generally have hardness in the range of 7-10 kg/cm^2. In case of trilayer tablets the hardness of the tablets was found to be 7.2 to 8.4 kg/cm^2. The friability of the formulations was found to be less than 1% and hence the tablets with lower friability may not break during handling on machines and or shipping. All the batches of the tablets complied with the weight variation limits as per the IP. The drug content in different formulation was highly uniform and the results are depicted in **Table 6**.

Table 6: Physical evaluation of Entacapone trilayer tablets

Formulation code	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	% Drug content
AF14	7.4±0.23	0.35	596±20	98.1
BF14	7.9±0.45	0.27	599±20	97.8
CF14	8.4±0.47	0.45	595±20	98.4
DF14	8.1±0.12	0.16	594±20	96.6

EF14	7.2±0.49	0.32	597±20	98.4
FF14	7.8±0.28	0.46	595±20	97.9
GF14	7.6±0.15	0.37	596±20	97.1
HF14	7.2±0.85	0.22	598±20	97.9

In vitro dissolution studies of Entacapone Trilayer tablets

The release of Entacapone from different formulations was carried out in phosphate buffer pH 6.8 and the results are depicted in Table. The trilayer tablets extended the drug release upto 24 hrs. The highest drug release was found in the formulation HF14 i.e 96.29% within 24 h. HF14 was found to be optimized formulation based on the dissolution and other evaluation parameters. The results are shown in **Table 7 & Figure 4**. The comparison of marketed product Entacapone (200mg) film coated tablet and optimized formulation HF14 was shown in **Figure 5.** The drug release from marketed product was 99% within 60min.

Table 7: In-vitro cumulative % drug release studies of Entacapone trilayer tablets

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	60.34±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	69.75±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

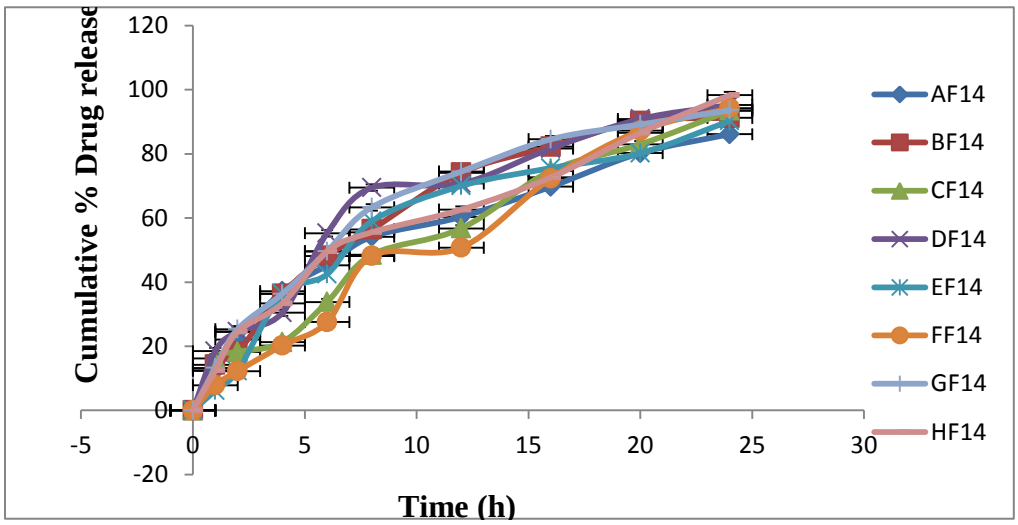

Figure 4: Comparative % drug release profile of AF14-HF14

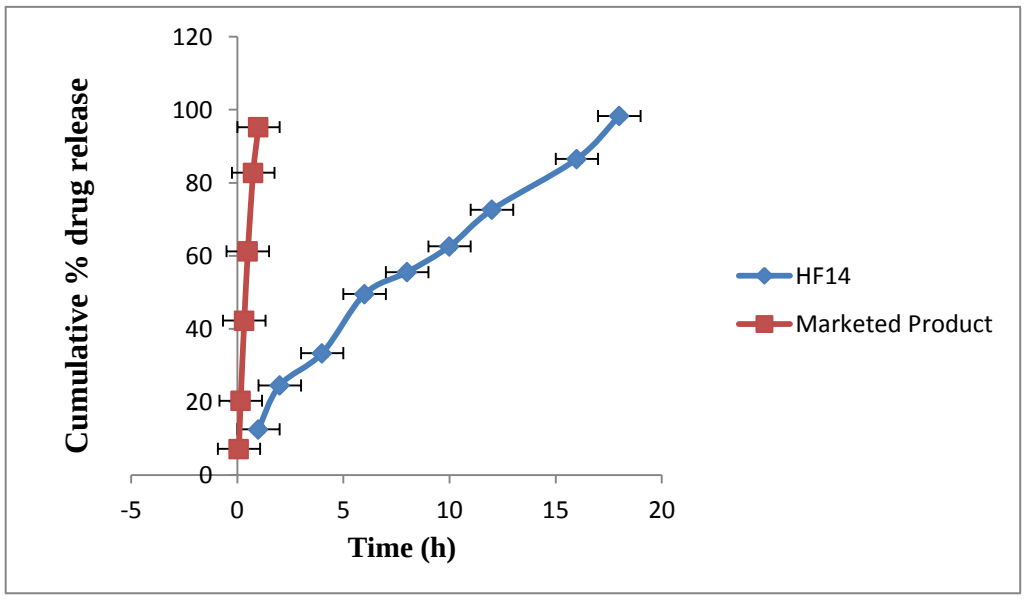

Figure 5: Cumulative percentage drug release of Entacapone from marketed product and optimized formulation HF14

Table 8: Drug release kinetics of optimized (HF14) and Marketed product

Formulation code	Zero order	First order	Higuchi model
HF14	0.979	0.717	0.913
Marketed product	0.806	0.968	------

In the present investigation drug release mechanism is best fitting to zero order and Higuchi model because regression coefficient was seen closest to 1 in these models which conforms diffusion assisted mechanism of release. The marketed product Entacapone (200mg) was explained by first order kinetics as the plot showed highest linearity (r^2=0.968) as the drug release was best fitted in first order kinetics.

CHARACTERIZATION

FT-IR

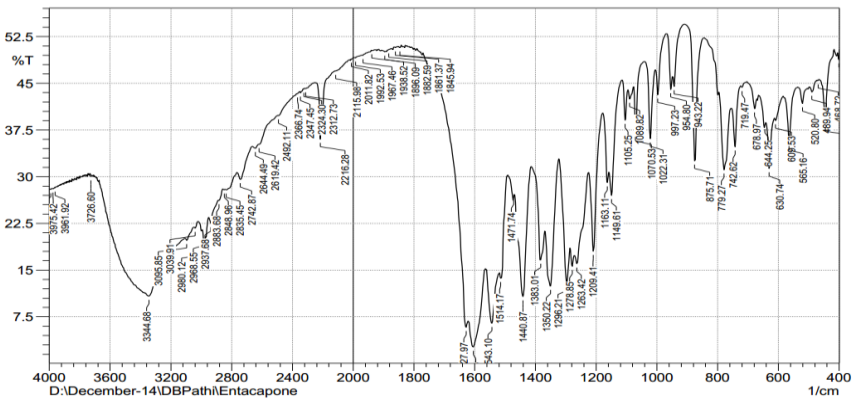

Figure 6: FT-IR spectrum of pure drug Entacapone

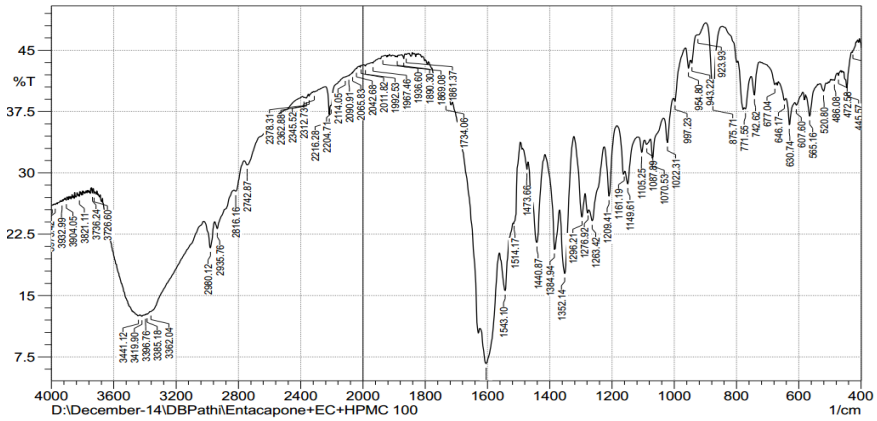

Figure 7: FT-IR spectrum of pure drug and other polymers

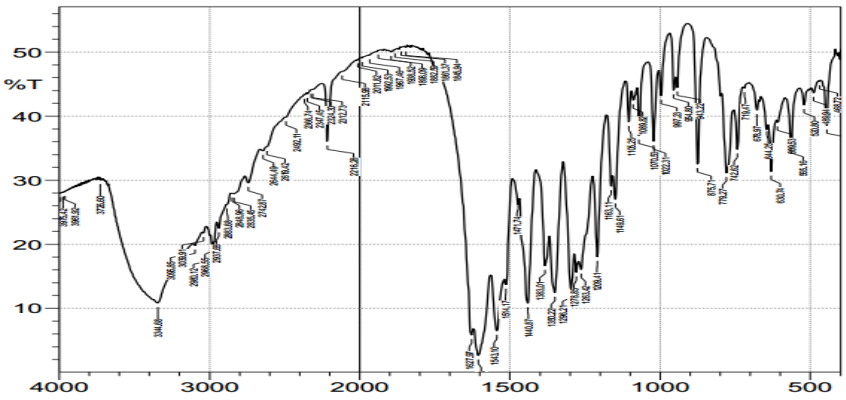

Figure 8: FT-IR spectrum of optimized formulation HF14

Overall there was no alteration in peaks of Entacapone pure drug **(Figure 6)** and optimized formulation **(Figure 7)**, suggesting that there was no interaction between drug & excipients. FT-IR spectrum of pure drug and other polymers are shown in **(Figure 8)**. There is additional peaks appeared or disappeared hence no significant changes in peaks of optimized formulation was observed when compared to pure drug indicating absence of any interaction.

SUMMARY AND CONCLUSION

It was concluded that trilayer matrix tablets of Entacapone can be successfully prepared by direct compression technique using different polymers combination. Based on the evaluation parameters, drug dissolution profile and release drug kinetics HF14 was found to be optimized formulation. The drug release from HF14 was found to fit Zero order of concentration independent and best fitted to Higuchi's model confirming to be diffusion assisted mechanism. The marketed product release was explained by first order kinetics by concentration dependent. These results also demonstrated the suitability of three-layered tablet formulation of Entacapone to provide controlled release for prolonged period of time and improved linearity for Entacapone in comparison to marketed product with conventional drug release profile in the management of Parkinson's disease.

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