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Formulation development and evaluation of Levodopa-Carbidopa orally disintegration tablets

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ABSTRACT

Levodopa- Carbidopa combination of orally disintegration tablet used in the treatment of parkinsonism was formulated and prepared by direct compression method and evaluated results were compared with marketed tablets for the better formulation than marketed products. Orally disintegrating tablets (ODTs) provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. This work describes the various formulation aspects, disintegrants employed along with various excipients and the technologies developed for ODTs (which include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and use of highly water soluble excipients), compatibility studies of Active Pharmaceutical Ingredient with the excipients, Post-compression techniques, evaluation tests, palatability studies, stability studies according to ICH guidelines for the various formulation done(F1-F10). Effect of superdisintegrants (such as microcrystalline cellulose, sodium starch glycolate and crospovidone) on wetting time, disintegration time, drug content, invitro release and stability parameters has been studied. Taste evaluation (palatability studies) was done for the formulation with the peppermint oil and evaluated for its better compliance than the other flavors used in the formulation. Taste and disintegration of optimized formulation (F5&F7) were found to be better than the marketed product. Drug release rate was more or less same as that of the marketed product. Direct compression was more preferred method since it is economical and includes less procedure steps than the other methods.

Key words: Orally disintegrating tablets, Super disintegrants, Direct compression, Levodopa, Carbidopa.

INTRODUCTION

Oral route of administration is most convenient for administrating drugs for systemic effect because of ease of administration and dosage adjustments. Swallowing conventional tablets can

be further hindered by conditions such as allergic reactions, and episodes of coughing [1]. A solid dosage form containing medicinal substance, which disintegrates rapidly usually within of seconds, when placed upon the tongue also called as quick disintegrating tablet, rapid disintegrating tablet, porous tablet, mouth dissolving tablet [2]. Tablet that is to be placed in the mouth where it disperses rapidly before swallowing**.** Absorption through the cheek allows the drug to bypass the digestive tract for rapid systemic distribution. Not all ODTs have buccal absorption and many have similar absorption and bioavailability to standard oral dosage forms with the primary route remaining GI absorption. However, a fast disintegration time and a small tablet weight can enhance absorption in the buccal area. The first ODTs disintegrated through effervescence rather than dissolution, and were designed to make taking vitamins more pleasant for children [3]. The ideal characteristic of oral disintegrating solid dosage form are Ease of administration, Taste of the medicament, Drug properties, Hygroscopicity, Friability, Taste masking:(sweet, salt, sour, bitter) [4]. The fast dissolving property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration [5]. Hence the basic approach to developing fast dissolving tablet include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water soluble excipients in the formulation [6]. This method was adapted to pharmaceutical use with the invention of micro particles containing a drug, which would be released upon effervescence of the tablet and swallowed by the patient [7]. Dissolution became more effective than effervescence through improved manufacturing processes and ingredients (such as the addition of mannitol to increase binding and decrease dissolution time) [8]. Conventional method used in preparation of orally disintegrating tablet includes: Freeze drying [9], tablet molding [10], and spray drying [11], mass extrusion [12], sublimation [13] and direct compression [14, 15].

The direct compression tablets disintegration and solubilisation are based on the single or combined dosage action of disintegrants, water soluble excipients and effervescent tablets. Addition of disintegrates in ODT's leads to quick disintegration and hence improves dissolution, which are optimized by the disintegrants concentration. Addition of disintegrants in ODT's leads, to quick disintegration of tablets and hence improves dissolution. In many ODT technologies based on direct compression, the disintergrants principally affect the rate of disintegration and hence the dissolution. Below critical concentration, tablet disintegration time is inversely proportional to disintegrants concentration. Above the critical concentration level, however, disintegration time remains approximately constant or even increases. Fast disintegration tablets can also be achieved by incorporating effervescent disintegration agents, which generates carbon dioxide. This phenomenon also resulted in partial taste masking of unacceptable taste of the drug**.**

Disintegrants are the substance added to the drug formulation that facilitates the breakup or disintegration of tablet or capsule content into smaller particles the dissolve more rapidly than in the absence of disintegrants. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1-10% by weight relative to the total weight of the dosage unit. Examples of superdisintegrants are crosscarmelose, crosspovidone, sodium starch glycolate which represent example of a cross-linked cellulose, cross-linked polymer and a cross linked starch respectively. Disintegrants are essentially added to tablet granulation for causing the compressed tablet to break or disintegrate when placed in aqueous environment. Incorporating disintegrants agents into tablet are three types internal addition (intragranular), external addition (extragranular), partly internal and external. The two-step method usually produces better and more complete disintegration than the usual method of adding the disintegrants to the granulation surface only. The active ingredients must be released from the tablet are broken into small pieces

and then produces a homogenous suspension is based on capillary action, high swellability, capillary action and high swellability, chemical reaction.

Levodopa is a metabolite precursor of doapamine. It is used to increase dopamine levels for the treatment of Parkinson's disease since it is able to cross the blood brain barrier, whereas dopamine itself cannot. After entering it is metabolized to dopamine by aromatic L-amino acid decaboxylase. It is standard clinical practice to co-administer a peripheral DOPA decaboxylase inhibitor carbidopa or benserazide and often a catechol-O-methyl transferse(COMT) inhibitor, to prevent synthesis of dopamine in peripheral tissue. Carbidopa inhibits aromatic-L-aminoacid decarboxylase (DOPA decarboxylase) an enzyme important in the biosynthesis of L-tryptophan to serotonin and in the biosynthesis of L-DOPA to Dopamine. It increases the plasma half-life of Levodopa from 50 minutes to 1 ½ hours. It thus prevents the conversion of L-DOPA to dopamine peripherally [16].

EXPERIMENTAL SECTION

Formulation of tablets was performed, in which each formulation contains 25 mg of Carbidopa and 250 mg of Levodopa (Table 1). Drug-excipients compatibility studies were performed (Table 2).

Table. 1 FORMULATION OF TABLET

Each formulation contains 25 mg of cabidopa and 250 mg of levodopa

Ingredients	Formulations									
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10
Mannitol EZ spray	390.5	408.5	460.5	488.5	400.5	-	477.5	476.5	457.5	478.5
Sorbitol	-	-	-	-	-	443.5	-	-	-	-
Sodium starch glysolate	100	130	150	-	-	-	-	-	-	-
Avicel PH 102	40	-	-	25	40	40	63.5	63.5	63.5	63.5
Crospovidine XL-10	-	-	-	130	200	120	100	100	100	100
Citric acid anhydrous	22	28	23	20	20	28	20	20	25	20
Sodium bicarbonate	25	20	30	20	23	32	23	27	20	22
Aspatamine	15	15	15	15	15	15	15	15	15	15
Flavor	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Sodium stearyl fumerate	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5
FDC blue	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Total	950	960	980	1000	1000	980	1000	1003	990	1000

Table. 2 DRUG-EXCIPIENTS COMPATIBILITY STUDIES

Excipients	Ratio	Description	
		Initial	Final
Cabidopa and levodopa-API	- - -	White to off white powder	White to off white powder
API-Avicel PH 102	1:5	Off white coloured powder	Off white coloured powder
API-Mannagem	1:5	Off white coloured powder	Off white coloured powder
API+ CrospovidoneXL	1:5	Off white coloured powder	Off white coloured powder
API+ Aspartamine	1:1	Off white coloured powder	Off white coloured powder
API+ Aerosil	1:1	Off white coloured powder	Off white coloured powder
API+ Magnesium stearate	1:1	Off white coloured powder	Off white coloured powder
API+ Peppermint flavor	1:1	Off white coloured powder	Off white coloured powder

Preparation of Tablets [17]

Tablets were prepared by the direct compression technique. It is the easiest method to manufacture tablets and this method involves the same process as that of conventional solid dosage forms such as weighing, screening, mixing, and compression.

- Weigh carbidopa, mannogem, levodopa and sieve through 35 mesh and mix foe 5 min.
- Weigh Avicel, Aspartamine, Crospovidone, Citric acid anhydrous, NaHCO3**,** Mint Flavor, Aerosil, and FDC blue individually.
- Citric acid anhydrous, NaHCO3**,** Mint Flavor is sifted through 60 #, FDC blue sifted through
- 80 #, and remaining excipients were sifted through 35# then added to the above mixture and mixed well.
- Weigh Sodium stearyl fumerate and sifted through 35# then added to the above mixture and mixed
- Compressed the tablet with 25 mm round punches

The various Pre-formulation studies (Table 3), Pre-compressional studies (Table 4) Solubility studies with 0.1 N HCL and water by using HPLC (Table 5) were performed on Carbidopa-Levodopa API. Stability studies are carried out according to ICH guidelines. These studies for tablets were carried out at 40^{O}C/75 RH. The optimized formulation was initially packed in a Aluminium blister pack containing 6 tablets in each strip. These strips were kept in stability chamber foe a period of two months and periodically evaluated for drug content (Table 5).

Table. 3 API CHARACTERIZATIONS

API	Angle of repose	Bulk density	Tap density	Carr's index
Levodopa	25.1	0.1	0.2	44.441
Carbidopa	25.32	0.1	0.2	44.161

Table. 4 EVALUATED RESULTS OF PRE-COMPRESSIONAL AND POST-COMPRESSIONAL PARAMETERS

PARAMETERS		F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10
Angle of repose		25.32	26.59	29.85	30.34	26.56	28.28	32.53	30.53	29.56	25.26
Bulk density		0.375	0.384	0.389	0.370	0.410	0.422	0.428	0.422	0.428	0.416
Tap density		0.526	0.545	0.535	0.517	0.601	0.601	0.611	0.625	0.576	0.588
Carr's index		28.75	31.25	27.27	28.39	31.50	30.55	28.57	32.39	34.61	29.16
Hausner' ratio		1.40	1.41	1.37	1.39	1.46	1.42	1.40	1.47	1.34	1.41
Thickness (mm)		5.02	5.05	5.02	4.98	5.04	5.06	5.03	5.02	5.02	5.08
Hardness(kg/cm^2) (average)		5.8	5.5	6.4	6.5	6.5	6.6	6.5	6.6	6.0	6.8
Friability(%)		0.05	0.06	0.05	0.44	0.05	0.50	0.05	0.23	0.1	0.02
Disintegration time(sec)		25-40	25-50	10-15	25-50	10-15	60-120	15-20	40-45	15-20	10-15
Wetting time(sec)		20	25	20	25	18	60	15	20	18	20
% Drug release in 45 min	Levodopa	100.12	99.81	99.87	99.41	99.89	98.47	99.89	101.6	99.63	100.2
	carbidopa	99.46	99.48	98.32	98.54	99.24	92.74	99.52	99.32	99.42	98.79
Content uniformity (%)		95.65	97.8	96.8	101.8	99.7	96.7	100.5	96.5	97.3	98.9

EVALUATION OF TABLETS

Compressed tablets were evaluated for the following parameters Weight variation test, Hardness test, Thickness and diameter test, Friability test, Disintegration test, Wetting time and Dissolution test.

Table. 5 STABILITY STUDIES OF THE SELECTED FORMULATION

Parameters		Initial		30days		60 days	
		F-5	F-7	F-5	F-7	F-5	F-7
Hardness		6.7	6.8	6.7	6.8	6.7	6.8
Thickness		5.04	5.03	5.04	5.03	5.04	5.03
Disintegration time		12	15	11	14	11	16
Friability		0.05	0.05	0.02	0.08	0.05	0.02
Assay	levodopa	101.4	99.9	100.2	99.9	100	99.7
	carbidopa	99.6	99.9	99.4	99.7	99.6	99.6
%drug Release In 45min	Levodopa	99.89	99.89	99.72	99.69	99.46	99.12
	carbidopa	99.24	99.52	98.93	99.21	98.42	98.98

Standard preparation

50 mg of Levodopa RS to 100ml volumetric flask, add accurately weighed Carbidopa RS, which the ratio with USP Levodopa RS that corresponds with the ration of Carbidopa to Levodopa in the tablets. Add 10 ml of 0.1 N Phosphoric acid. Warm gently to dissolve the standards. Dilute with water to volume, and mix.

Sample preparation

Weigh and finely powder not fewer than 20 tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg of Levodopa, to a 100ml volumetric flask, add 10ml of 0.1N Phosphoric acid dilute with water to volume and mix.

Chromatographic system

The liquid chromatography is equipped with a 280nm detector and a 3.9-mmx 30-cm column that contains packing L1. The flow rate, about 2ml per minute, is adjusted until the retention times for Levodopa and Carbidopa are about 4 minutes and 11 minutes respectively. Chromatograph 5 replicate injections of the standard preparation and record the peak responses a directed for procedure, the relative standard deviation is not more than 2.0% and the resolution factor between Levodopa and Carbidoap is not less than 6.621

Procedure:

Inject 20 micro liters of the standard and sample preparation in to the chromatograph and run it 4 minutes for Levodopa and 11 minutes for Carbidopa. Record the chromatograms and measure the peaks responses. For the assay same conditions are followed as like dissolution.

Sample preparation:

Weigh and finely powder not fewer than 20 tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg of Levodopa to a 100 ml volumetric flask and add 10 ml 0.1N phosphoric acid dilute with water to volume and mix.

Content uniformity

Sample preparation:

Transfer 1 tablet into 100 ml volumetric flask. Add about 75 ml of diluents. Filter the sample solution through 0.45 micron

RESULTS AND DISCUSSION

The present invention was undertaken to formulate Carbidopa-Levodopa combination into orally disintegrating tablet formulation using direct compression technique for the treatment of orally Parkinson's disease.

The each tablet formulation contains 25 mg of carbidopa and 250 mg of levodopa (Table 1), Drug excipients compatibility studies were performed for the formulation with different excipients (Table 2). The API characterization showed that the Carr's index was more in Levodopa than Carbidopa, Bulk density and True density was similar for both the drugs, Angle of repose showed approximately same values (Table 3)

All formulation from F1-F10 batches had been subjected to various evaluations and from that, F1, F2, F3 with SSG at concentration of 10%, 13%, 15% respectively were not satisfactory with the disintegration time and hardness (Table 4). F4 with crospovidone 13% also failed with DT (disintegrating time) of 25-50 sec. F5 with crospovidone 20% produced a satisfactory results with DT of 23 sec. F6 with sorbogen was also not satisfactory. F7 with mannogen replacing sorbogen produced a satisfactory results with DT of 25 sec and hardness 6.5-7.2 Kg\cm^2. F8 with mannogen and crospovidone was also failed and F9&F10 was also failed with Avicel as super disintegrants. Out of ten formulation F5&F7 were satisfactory with their hardness and DT. Stability studies were performed for initial, 30 days and 60 days period (Table 5) and solubility study of the API also performed which showed solubility in 0.1 N HCl was more than in water (Table 6).

Table. 6 SOLUBILITY STUDIES OF THE API

API	Time (at 45 min)	% drug release Sample 1	% drug release Sample 2	Average
Carbidopa in water	45	18.4	18.6	18.5
Carbidopa in 0.1 N HCL	45	102.2	99.6	100.9
Levodopa in water	45	20.7	20.4	20.6
Levodopa in 0.1 N HCL	45	100.2	99.98	100.9

CONCLUSION

Directly compressed tablets were prepared with different excipients for the present work. Tablets were compressed using 15mm round punches, a 12 station rotary compression machine. Among the ten formulation F-5&F-7 were the better than marketed formulation. Taste evaluation was studied with ten human volunteers on the peppermint oil formulation & resulted as good. Direct compression was more preferred economical and includes less procedure steps than other methods

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