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FORMULATION AND EVALUATION OF FLOATING CAPSULE OF ANTIPARKINSON DRUGS

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ABSTRACT

In the present study hydrodynamically balanced system of antiparkinson drugs was developed as single unit floating capsule. Various grades of low density polymers were used for formulation of this system. The formulation was prepared on the basis of in vitro buoyancy and in vitro drug release profile in 0.1N HCl. Buoyancy study of formulated capsule was achieved over a period of 12 hrs. The effect of additional low density grade polymers on drug release pattern and swelling index were also studied. The effect of change in polymer concentration and effect of different grades of polymer with the use of intra granularly and extra granularly were also studied. Initial 3 batches with the use of direct mix was not showing acceptable flow property with different diluents. The granulometry property was acceptable with the wet granulation method. Dissolution profile and swelling index were matched with the reference by different grades of polymers. But formulation failed in stability so strategy was changed to pelletization technique. Drug was granulated with binder and drug granules were coated with the HPMC 6cps to avoid direct contact of drug with atmosphere. Other excipients like BHA, BHT and citric acid were added to reduce impurities. Capsule prepared with HPMC K15 M, HPMC K100 M and citric acid gave best drug release with controlled impurities.

Keywords: Hydrodynamically balanced system; Buoyancy; HPMC; BHA; BHT; citric acid; Low density polymers.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of the drug to the proper site in the body to achieve promptly, and then maintain, the desired drug concentration. The drug delivery system should deliver drug at a rate dictated by the needs of the body over the period of treatment. The present study was aimed to formulate and evaluate the Floating capsule of Antiparkinson drugs by using rate controlling polymer in order to improve patient compliance, Reduce dosing frequency and Increase bioavailability of the drug. Parkinson's disease (PD) belongs to a group of conditions called motor system disorders, which are the result of the loss of dopamine-producing brain cells. DCPT035 the metabolic precursor of dopamine, is the single most effective agent in the treatment of PD.

DCPT035 dose crosses the blood-brain barrier and is decarboxylated to dopamine. This newly formed dopamine then is available to stimulate dopaminergic receptors. DCPT035 is decarboxylated to dopamine before it reaches the brain, and dopamine is unable to cross the blood-brain barrier. DCPT036 inhibits this decarboxylation, allowing the DCPT035 to enter the brain. Because DCPT036 does not enter the CNS, DOPA decarboxylase is uninhibited there and metabolizes the DCPT035 into useful dopamine. Care must be taken while handling DCPT036 because it is hygroscopic. It is gradually colored by light[55] so experimental work need to be done in presence of sodium lamp and humidity need to be maintained low. To develop a stable formulation of DCPT035/DCPT036 with optimization of polymer Hypromellose, with different concentration to achieve control release formulation with floating characteristic

Table:1: Formulation

Sr. No.	Ingredients	001*	002*	003*	004*	005*	006*	014*	015*	016*	017*
1	DCPT035	100.0	100.0	100	100	100.00	100.00	167.00	158.00	158.00	158.00
2	DCPT036 HCl eq to DCPT036	28.5	28.5	28.5	28.5	28.50	28.50	36.00	56.0	56.0	56.0
3	Dicalcium Phosphate anhydrous	-	-	-	54.5	24.00	14.00	-	-	-	-
4	Povidone K30	-	-	-	12	15.00	15.00	-	-	-	-
5	Mannitol 25	80.5	-	-	-	-	12.00	-	-	-	-
6	Avicel	-	-	55	-	-	-	-	-	-	-
7	Mannitol (Pearlitol SD 200)	-	60.5	32.5	20	17		12.50	1.50	1.50	1.50
8	Hydrogenated vegetable oil	40.0	40.0	28	28.5	36.00	36.00	-	-	-	-
9	HPMC (metolose 90 SH 100000SR)	80.0	80.0	45	45	75	90.00	21.00	21.00	21.00	21.00
10	HPMC K15M	-	-	-	-	-	-	60.00	60.00	60.00	60.00
11	BHA	-	-	-	-	-	-	-	0.05	-	0.05
12	BHT	-	-	-	-	-	-	-	0.05	-	0.05
13	Citric acid	-	-	-	-	-	-	-	-	0.6	0.6
14	Talc	6.0	6.0	6	6.5	6.5	6.50	1.50	1.50	1.50	1.50
15	Magnesium Stearate	5.0	5.0	5	5	5	5.00	2.00	2.00	2.00	2.00
16	IPA	-	-	-	qs	qs.	qs.	-	-	-	-
	Total	340	320	300	300	300	300	300	300	300	300

Result and Discussion:

Granulometry analysis data such as bulk density, tapped density, Carr's index and Hausner's ratio are as per table no 2.

Table: 2 Granulometry analysis data

B. No.	B.D (gm/ml)	T.D (gm/ml)	% CI	HR	AOR
001	0.31	0.52	40.38	1.67	45.5
002	0.35	0.54	35.18	1.54	42.1
003	0.38	0.58	34.48	1.53	40.3
004	0.36	0.54	33.33	1.5	38.4
005	0.4116	0.5908	30.33	1.43	36.89
006	0.4056	0.5832	30.45	1.43	35.52
014	0.4896	0.6923	29.27921	1.414011	0.4896
015	0.5732	0.6647	13.76	1.159	32.43
016	0.5892	0.6782	13.12	1.151	31.87
017	0.5789	0.6621	12.56	1.14	33.45

Weight variation: From different location 20 capsules were taken and checked for weight variation. All the data of Weight variation is as per following table no 6.4.C.

Table: 3 Weight variation data

Batches	Average weight of capsule*
001	362-483.8
002	342-436
003	342-432
004	368.3-383.4
005	368.3-383.4
006	368.85-381.36
014	369.14-384.6
015	368.75 - 379.78
016	364.72 - 382.68
017	369.22 - 384.16

Dissolution Profile: Dissolution Profile was carried out using basket type of dissolution apparatus at 100 rpm in 900mL of 0.1N HCl used as dissolution media.

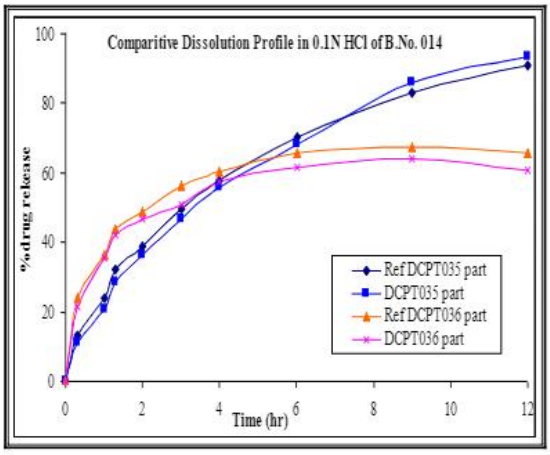

Figure: 1: Comparative dissolution profile in 0.1 N HCl of B.No. 014

Swelling index: Swelling index was measured by keeping a capsule in dissolution media after measuring an initial weight. Measure a capsule weight after particular intervals. From the weight of capsule, measure % water uptake.

Table: 4: Swelling index of B. No.: 014

	Initial weight	Weight After particular hours					
		1 hr	3 hr	4 hr	6 hr	7 hr	8 hr
Weight of Reference*	421.8	621.9	886.2	860.6	814.5	779.9	760.8
% WU of Reference #	-	47.4	110.1	104.0	93.1	84.9	80.4
Weight of B.No.014*	377.2	723.5	813.7	765.3	738.9	708.3	687.4
% WU of B.No.014 #	-	91.8	115.7	102.9	95.9	87.8	82.2

*** Quantity in mg**

 # Quantity in %

Stability data: We need to control the impurities of DCPT036 so this batch was kept for stability study in accelerated stability conditions for 7, 15 days and the results are given below.

Table: 5: Stability data of B. No.: 014

Condition/ Period	Related Impurities of *DCPT036 part* (%)			
	A	*B*	*C*	Total
Initial	0.05	0.47	0.03	**0.55**
40^0C 75%RH 7 days	0.07	0.62	0.04	**0.73**
40^0C 75%RH 15 days	0.11	0.81	0.06	**0.98**

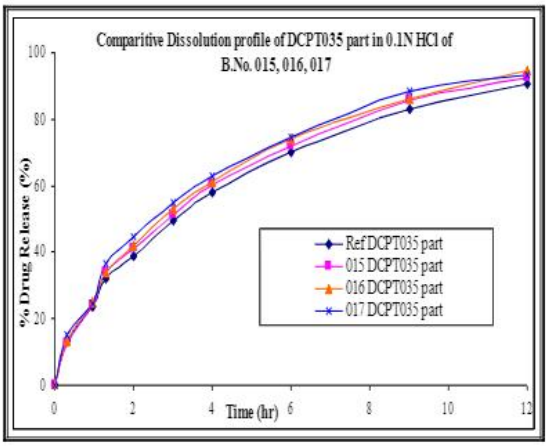

Figure: 2: Comparative dissolution profile of DCPT035 part in 0.1 N HCl of B.No. 015, 016, 017.

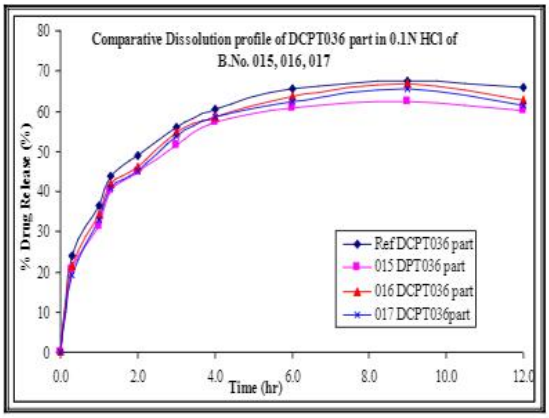

Figure: 3: Comparative dissolution profile of DCPT036 part in 0.1 N HCl of B.No. 015, 016, 017.

Swelling index: Swelling index was measured by keeping a capsule in dissolution media after measuring an initial weight. Measure a capsule weight after particular intervals. From the weight of capsule, % water uptake was measured.

Table: 6: Swelling index of B. No.: 015, 016, 017

	Initial weight	Time (hr)					
		1 hr	3 hr	4 hr	6 hr	7 hr	8 hr
Weight of Reference*	421.8	621.9	886.2	860.6	814.5	779.9	760.8
% WU of Reference #	-	47.4	110.1	104.0	93.1	84.9	80.4
Weight of B.No.015*	375.1	754.8	849.2	764.6	731.6	682.9	674.6
% WU of B.No.015 #	-	101.2	126.4	103.8	95.0	82.1	79.8
Weight of B.No.016*	376.8	758.9	840.3	758.9	721.3	679.5	668.9
% WU of B.No.016 #	-	101.4	123.0	101.4	91.4	80.3	77.5
Weight of B.No.017*	374.4	768.3	831.3	749.9	714.3	678.9	662.7
% WU of B.No.017 #	-	105.2	122.0	100.3	90.8	81.3	77.0

*** Quantity in mg**

 # Quantity in %

Stability data: We need to control the impurities of DCPT036 so this batch was kept for stability study in accelerated stability conditions for 7, 15 and 30 days and the results are shown below.

Table: 7: Stability data of B. No. 015, 016, 017

B.No.	Period at 40ºC/75% RH	Related Impurities (%) DCPT036			
		A	*B*	*C*	Total
015	Initial	0.05	**0.43**	0.03	**0.51**
	7 days	0.06	**0.44**	0.03	**0.54**
	15 days	0.07	**0.46**	0.04	**0.57**
	30 days	0.07	**0.47**	0.04	**0.58**
016	Initial	0.05	**0.46**	0.03	**0.54**
	7 days	0.07	**0.55**	0.04	**0.66**
	15 days	0.09	**0.65**	0.05	**0.79**
	30 days	0.09	**0.78**	0.05	**0.94**
017	Initial	0.05	**0.43**	0.03	**0.51**
	7 days	0.06	**0.46**	0.03	**0.52**
	15 days	0.07	**0.47**	0.04	**0.58**
	30 days	0.07	**0.52**	0.04	**0.63**

CONCLUSION

From literature survey, DCPT036 needs special care when formulating into pharmaceutical preparations due the physical stress associated with formulating processes which can increase the rate of decomposition of DCPT036. Indeed, factors that influence the stability of DCPT036 formulations are light, heat and moisture. It is also affected at higher and neutral pH. So for formulation containing DCPT036 needs special care. So formulation work must be done at low humidity and in presence of sodium lamp. DCPT036 is been affected by higher pH so drug must release in stomach. So this formulation was planned to float in gastric fluid and drug release at gastric fluid. This formulation can be prepared in the form of floating capsule by use of polymers with density lower than that of gastric fluid. We need to match dissolution with reference. We have to develop a formulation in capsule dosage form which contains stable DCPT035 and DCPT036 with effective and safe for parkinson.

Preformulation study and Preliminary work had been performed. Reference dosage form is capsule, in which dissolution of capsule is achieved in 12 hour. So, these physical and chemical criteria of references capsule will be used for the comparisons of our trials to develop a formulation contains stable DCPT035 and DCPT036.Preliminary trials included three trials for formulation development by direct mixing and filling capsule. In this trial, flow of

the blend was not achieved and found a weight variation problem. To improve the flowability of blend, different diluents were used. In first trial mannitol 25 was used which was replaced with pearlitol SD 200 in 2nd trial. In 3rd trial combination of pearlitol and Avicel pH 112 were used. Granulometry property was improved but still not acceptable. So wet granulation method was tried in next batch. Formulation strategy kept same according to B.No 014. Change made in granulation of DCPT036 in B.No 015, 016 and 017. In this step BHA, BHT and Citric acid were dissolved in solvent as per the formula while preparing the binder solution. This batch was kept for the stability study. Results of stability data shown that B.No 015 with BHA and BHT got failed. But the data of stability study of B.No 016, with citric acid were good. Impurities were controlled by citric acid. So this batch was decided as the optimized batch.

Whole investigation summarized that capsule prepared with incorporating drugs with other excipients in B.No 016 shown good stability and floating action of capsule with highest similarity with Reference product.

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