The Pharma Innovation

ISSN: 2277- 7695
CODEN Code: PIHNBQ
ZDB-Number: 2663038-2
IC Journal No: 7725

Received: 09-02-2013
Accepted: 06-04-2013

Vol. 2 Issue 3 2013
Online Available at www.thepharmajournal.com

THE PHARMA INNOVATION - JOURNAL

Formulation and Evaluation of Diphenhydramine Hcl Rapid Release Gelcaps 25 Mg

Margret Chandira*[1], A. Pasupati[1], H.V. Adinarayana Innamuri[1], M. Komala[2], N.K. Agarwal[3], Debjit Bhowmik

1. Vinayaka Missions College of Pharmacy, Salem, Tamilnadu, India
   [E-mail: debjit_cr@yahoo.com]
2. Mohamed Sathak A.J. College of pharmacy, Chennai, India
3. Nimra college of Pharmacy, Nimranagar, Vijayawada, Andhra Pradesh, India

The objective of the present study was to develop Rapid Release Gelcaps of Diphenhydramine HCl, for treatment of Allergic symptoms and irritant cough. The Rapid Release gelcaps were prepared by Direct compression method using Pregelatinised maize starch and croscarmellose sodium in various concentrations. The granules showed satisfactory flow properties and compressibility. All the 8 formulations showed acceptable pharmacopoeial standards. The result of formulation B8 (40 mg Pregelatinised maise starch and 12 mg Croscarmellose sodium) Rapid Release of Diphenhydramine Hcl. Successful formulation was found stable after evaluation for physicochemical parameters when kept for 30 days at room temperature, 40^0C ± 2 & 75 % RH and 2-8 ^{0}C. It concluded that gelcaps containing Diphenhydramine HCl (40 mg Pregelatinised maise starch and 12 mg Croscarmellose sodium) provide a better option for Rapid release of drug.

Keyword: Diphenhydramine HCl, Rapid Release Gelcaps, Pregelatinised Maise Starch, Croscarmellose Sodium.

1. Introduction

The best new therapeutic entity in the world is of little value without an appropriate delivery system. Tablet delivery system can range from simple immediate release formulations to complex extended or modified release dosage forms. The most important role of drug delivery system is to get the drug delivered to the site of action in sufficient amount & at the appropriate rate. However it should meet other important criteria such as physical & chemical stability, ability to be mass-produced in a manner that assures content uniformity.To formulate and evaluate the DIPHENHYDRAMINE HCl rapid release gel caps by using direct compression method.To develop a rapid release dosage form (gel caps) of Diphenhydramine HCl gel caps.To develop and assess the feasibility of using a Direct compression manufacturing method for large scale production of Diphenhydramine HCl rapid release gelcaps. To assess the key components that affect drug release from dosage forms produced by direct Compression and therefore empirically optimize dosage form performance. The objective of the present study is to develop a pharmaceutically stable and robust formulation of Diphenhydramine HCl rapid release gelcaps 25mg comparable with innovator. To achieve this goal various prototype trials are taken & evaluated with respect to various quality parameters. The formulation shall be finalized by comparing the in - vitro dissolution profile with that of the innovator in various pH media.

2. Materials and Methods

Diphenhydramine HCl Procured from Wanberry Pharmaceuticals, MCC (102Grade) purchased from Mingtai Pharmaceutical pvt ltd, Pregelatinized Maize Starch, Croscarmellose sodium purchased from Roquette Freres, Colloidal silicon dioxide purchased from Cabott Sanmar Ltd

2.1 Materials Used Manufacturing Procedure:-

Direct Compression:

Steps:

2.1.1. Sifting and blending: Delump Diphenhydramine HCl using multi mill with 2.0 mm screen at medium speed. Sift weighed quantuities of Diphenhydramine HCl, cross carmellose sodium, micro crystalline cellulose (102 grade), pre gelatinised maize starch, micro crystalline cellulose (102grade) and colloidal silicon dioxide through #40 mesh. Load into the blender and blend for 15 min at 8 rpm. Sift stearic acid through #40 mesh and add to the above blend and blend for 5 min. at 8 rpm.

2.1.2. Compression: compress granules into tablets using 15.95×5.28 mm punches at an average weight of 400 mg per tablet.

2.1.3. Coating: Preparation of coating suspension:

Take purified water into a suitable vessel stir to form vortex. Add coating material aquarius bkp 19538 gray into vortex. Increase the stirrer speed if required to maintain the vortex. After adding of coating material reduces the stirrer speed so that no vortex should form. Continue stirring for 30-45 min at slow speed.

Coating process:

Load core tablets into coating pan. Pre heat the bed to about 45°C, set the below parameters.

Inlet temp: 55°C -60°C
Exhaust temp: 40°C-50°C
Atomization air pressure: 1.0 -2.0 bar
Pan speed: 1-6 rpm
Gun to bed distance: 10-15 cm
Spray rate: 6g/min

Start the spraying of coating suspension through peristaltic pump as per given parameters. Maintain the exhaust temperature between 40°C-50°C throughout the spray. Dry the tablets for 5-10 min.

2.1.4. Encapsulation: Get the gray colour coated tablets encapsulated on press fit capsulation machine. Maintain room humidity between 45%-55% and temperature between 23°C-27°C during encapsulation.

Pre Comression Parameters

A) Bulk Density:

Bulk density is defined as the mass of powder divided by bulk volume, It is calculated using the following equation:

Bulk density = weight of sample taken /volume noted

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured. Then the cylinder was dropped at 2-second intervals onto a hard wooden surface three times, from a height of one inch. The volume was recorded and the bulk density was calculated.

B) Tap Density:

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured. Then the surface was carefully smoothed and the volume was measured. Tap density was calculated by measuring final volume (V_f) after 50 taps on wooden surface from 6 inch height and was expressed in g/cm^3.

$$\text{Bulk density} = W/V_o$$

$$\text{Tapped density} = W/V_f$$

where,
V_o = initial volume.
V_f = final volume.

Where,
h = height of pile.
r = radius of the base of the pile.
θ = angle of repose.

2.2 Post Compression Parameters

All the prepared core tablets were evaluated for following official and unofficial parameters.

- Weight Variation
- Thickness
- Hardness Test
- Friability Test
- Assay
- In-Vitro Release Study

A) Weight Variation:

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage and none deviate by more than twice the percentage.

2.3 Percentage Deviation Allowed Under Weight Variation

Table 4: Percentage deviation allowed under weight variation test.

Percentage deviation allowed under weight variation test.	
Average weight of tablet (Xmg)	**Percentage deviation**
130 mg or less	10
130mg to 324 mg	7.5
more than 324 mg	5

B) Thickness:

Three tablets were randomly selected from each batch and there thickness was measured by using vernier calipers. Thickness of three tablets from each batch was measured and mean was calculated.

C) Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kp. Three tablets were randomly picked and hardness of the tablets was determined.

D) Friability: Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,

% F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution

Table 2: API Characterisation API Characterisation:

S.No	Property	Value
1	Angle Of Repose	47.73^0
2	Bulk Density (g/ml)	0.35
3	Tapped Density (g/ml)	0.7
4	Hausners Ratio	2.0
5	Compressibility Index	50
6	Assay (on dried basis)	99.67

Standard Curve of Diphenhydramine Hcl:

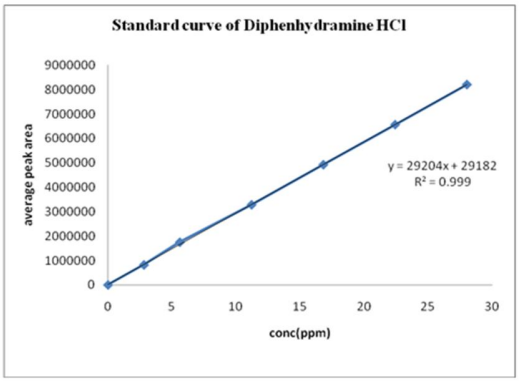


Fig.1. Standard curve of Diphenhydramine HCl

2.4 Composition Formulas of All Batches:

Table 4: composition formulas of all batches

S.No.	Ingredients	Qty (mg/tab)					
		B1	B2	B3	B4	B5	B6
1	Diphenhydramine HCl	25	25	25	25	25	25
2	Avicel pH-102	333.8	323.8	313.8	303.8	305.8	301.8
3	PGMS	20	30	40	50	40	40
4	Croscarmellose sodium	---	---	---	---	8	12
5	Aerosil	1.2	1.2	1.2	1.2	1.2	1.2
6	Stearic Acid	12	12	12	12	12	12
7	Talc	8	8	8	8	8	8

2.5 Evaluation of Granular Blend:

Table 5: Evaluation of granular blend

B.NO	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (^{0})
B1	0.430	0.690	37.60	1.60	29.4^0
B2	0.408	0.700	41.71	1.71	32.7^0
B3	0.460	0.608	24.34	1.32	31.6^0
B4	0.483	0.600	19.50	1.24	28.4^0
B5	0.425	0.681	37.59	1.60	27.9^0
B6	**0.403**	**0.625**	**35.52**	**1.55**	**33.9^0**

2.6 Comparative Data of Core Tablets Parameters:

Table 6: Comparative data core tablets parameters

B.NO	Average Weight (mg)	Thickness (mm)	Hardness (kp)	DT (min)	Assay (%)
B1	406.50	5.18-5.21	9.0-11.1	2'05"	99.49
B2	408.70	5.17-5.22	9.4-11.6	1'45"	99.67
B3	404.70	5.15-5.20	9.3-10.4	1'09"	99.53
B4	403.40	5.17-5.22	9.6-10.8	0'55"	99.98
B5	403.50	5.14-5.20	9.5-10.5	0'35"	99.32
B6	402.80	5.19-5.20	9.6-10.8	0'21"	99.78

2.7 Comparative Dissolution Profiles of Core Tablets B1-B4:

Table 7: Comparative dissolution profiles of core tablets B1 to B4

Time (min)	B1	B2	B3	B4
0	0	0	0	0
2	10.2	11.9	15.1	22.2
4	20.5	23.3	26.8	34.5
6	31.62	34.4	38.73	46.6
10	45.3	49.1	52.7	58.4
15	51.7	58.1	62.8	66.7
30	63.3	69.6	73.8	79.1

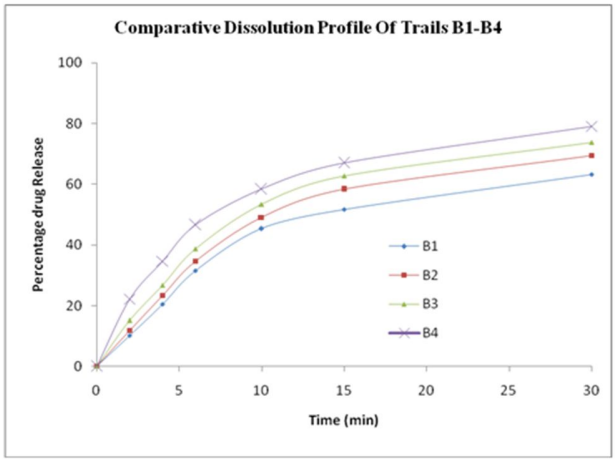


Fig 2: Comparative dissolution Profiles of trails B1-B4

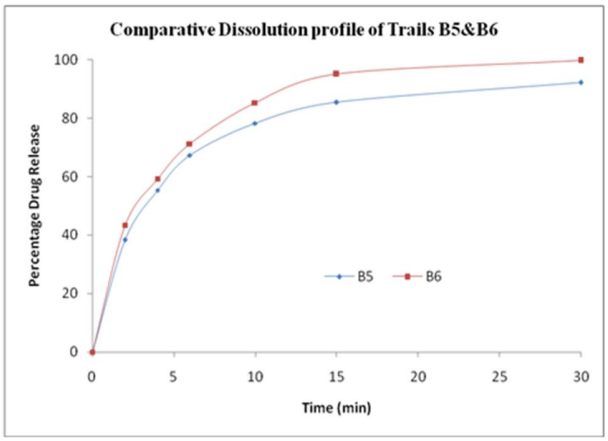


Fig 3: Comparative dissolution Profiles of trails B5&B6

2.8 Comparative Dissolution Profiles of Coretablets B5&B6:

Table 8: Comparative Dissolution Profiles Of Core Tablets B5 To B6

Time (min)	B5	B6
0	0	0
2	37.9	43.3
4	54.8	59.4
6	67.30	71.51
10	78.4	85.2
15	84.8	94.4
30	92.5	99.8

2.9 Formula for Coating Trail (B7):

Table.10: Formula for coating trail

S.NO	INGREDIENTS	Qty/tab (mg)
1	Diphenhydramine HCl	25
2	Avicel pH-102	301.8
3	PGMS	40
4	Croscarmellose sodium	12
5	Aerosil	1.2
6	Stearic Acid	12
7	Talc	8
8	Coating material	8
9	Purified water	72

2.10 Evaluation of Coated Tablets and Rr Gel Caps

Table 11: Evaluation Of Coated Tablets And Rr Gelcaps

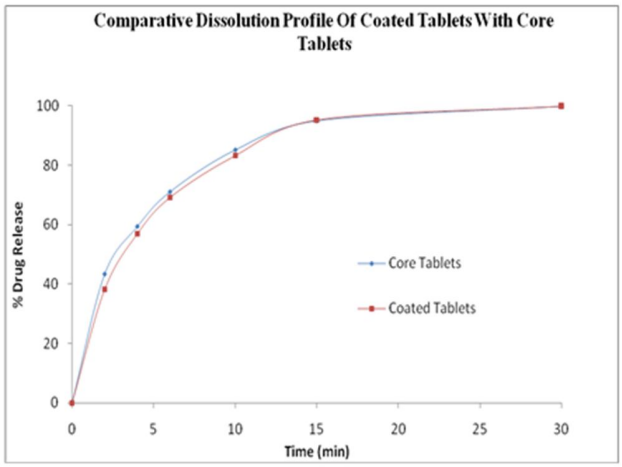
S.NO	Parameter	Coated tablets (B7)	RR gelcaps (B8)
1	Average weight (mg)	410.4	435.2
2	Thickness (mm)	5.21-5.24	--
3	Hardness (kp)	9.9-11.4	--
4	DT (min)	0'25"	0'55"
5	Assay	99.56	99.44
6	Locking length	--	16.15-16.30

2.11 Comparative Dissolution Profile of Coated Tablets with Core Tablets:

Table 12: Comparative dissolution profile of coated tablets with core tablets

TIME (MIN)	PERCENTAGE RELEASE	
	CORE TABLETS (B6)	COATED TABLETS (B7)
0	0	0
2	43.4	40.0
4	59.3	57.0
6	71.1	69.34
10	85.2	83.3
15	95.0	95.5
30	99.7	99.8

Fig 4: Comparative Dissolution Profile of Coated Tablets With Core Tablet



2.12 Comparative Dissolution Profile of Rr Gelcaps with Core Tablets:

Table.16: Comparative dissolution profile of rr gelcaps with core tablets

Time (MIN)	Percentage Release	
	Core Tablets (B6)	RR GELCAPS (B8)
0	0	0
2	43.4	35.3
4	59.3	57.2
6	71.1	71.42
10	85.2	85.7
15	95.0	95.6
30	99.7	99.9

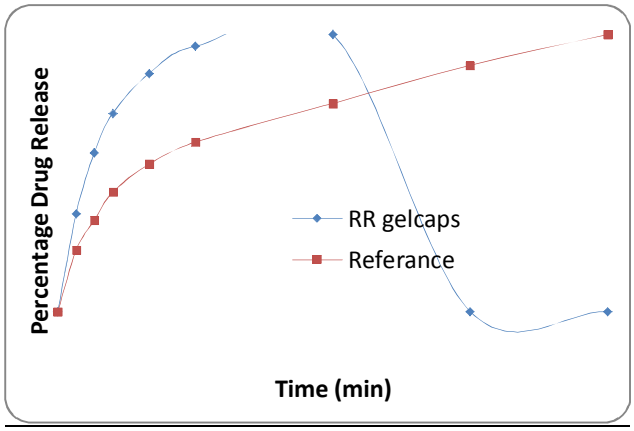
2.13 Comparative Dissolution Profile of Rr Gelcaps with Reference:

Table 17: Comparitive dissolution profile of rr gelcaps with reference

Time (Min)	Percentage Release	
	Reference	RR GELCAPS (B8)
0	0	0
2	22.12	35.3
4	32.98	57.2
6	43.01	71.42
10	53.14	85.7
15	60.97	95.6
30	74.90	99.9
45	88.54	-----
60	99.8	-----

2.14 Comparative Dissolution Profile of Rr Gelcas with Referance

Fig 14: Comparative dissolution profile of rr gelcaps with reference



2.15 Stability Studies

Table 17: Stability studies of optimized formulation B8

S.NO	Result→ Test ↓	Stability Specification	40°C/75%RH			2-8°C	
			Initial	15 Days	30 Days	15 Days	30 Days
1	Description	Encapsulated gray colour tablets with white opaque and pink opaque hard gelatin shells	Complies	Complies	Complies	Complies	Complies
2	Average wt :	355.0mg-392.4mg	368.2	370.2	375.7	380.5	380.2
3	Disitegration time (min)	Nmt 15min	0'58	1'35"	1'55"	2'09"	2'09"
4	Dissolution by HPLC	NLT 85% of the labeled amount of drug dissolved in 30 mins	99	97.5	98.4	96.9	95.5
5	Assay By HPLC	Between 90.0%-110.0% of label Amount.	100.7	99.8	99.5	99.1	98.1

2.16 Dissolution Profile of Reference

Table 1: Dissolution Profile of Reference

Time (min)	% Drug release
0	0
2	22.12
4	32.98
6	43.01
10	53.14
15	60.97
30	74.9
45	88.54
60	99.8

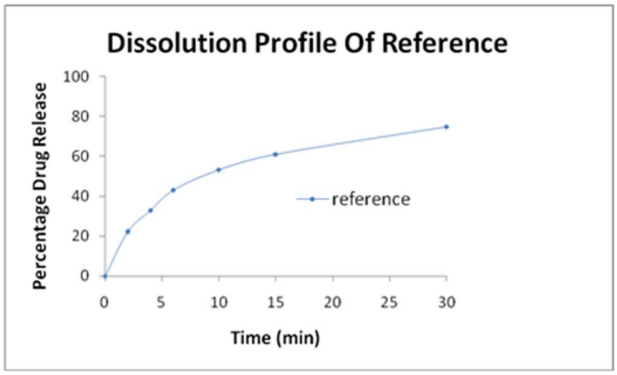


Fig 3: Dissolution Profile of Reference

3. Conclusion

The present work was an attempt to formulate and evaluate Rapid Release gelcaps of an anti-histamine drug Diphenhydramine HCl. In the present study direct compression was used to formulate core tablets.Diphenhydramine HCl (BCS Class-I) was chosen for Allergic symptoms and irritant cough because it has pKa of about 8.98 and it is rapidly absorbed after oral administration. Hence it is an ideal candidate to formulate Rapid release gelcaps.The Rapid release gelcaps were formulated by Directcompression method using croscarmellose sodium as a superdisintegrant in different concentrations like 2% and 3%, 10%concentration of pregelatinised starch in combination of Avicel used as disintegrant. The pregelatinised starch also used as binder to attain hardness (8-12). Total eight formulations (B1-B8) were prepared and evaluated for weight variation, thickness, friability, hardness, disintegration time, assay and in vitro dissolution study.The results of all formulations for weight variation, thickness, friability, hardness, disintegration time, and assay were found to be with in USP limits. The disintegration time for all formulations was found to be less than 2 min. In vitro dissolution studies showed that more than 90%of the drug released from all formulations with in 30 min. The B6 formulation containing croscarmellose sodium at in concentration of 3% showed minimum disintegration time of 21 seconds and 99.7% drug was released within 30 min when compare to other formulations.The core tablets were coated and the coated caplets were encapsulated by using hard gelatin shells by express fit method for their elegance and easy of swallowing. The invitro release of Rapid release gelcaps was compared with core tablets and found that there is no significant change in their release of drug. It indicates that Encapsulation doesn't effect the release of drug from formulation.The optimized formulation (B8) was compared with Reference product, from the Dissolution studies, it was confirmed that the drug release from (B8) was 99.9% within 30 min, where as the drug release from reference product was 99.8% at 60 min.Stability studies for optimized formulation B8 was carried out at 2-8^{0}C, at 40^{0}C/75%RH. There was no significant variation found in physical appearance, assay, and disintegration time of the Rapid release gelcaps.It was concluded that in direct compression method, croscarmellose sodium was best super disintegrant. Pregelatinised starch in combination of avicel was found to be disintegrant as well as binder. Further investigations are needed to confirm the in vivo efficiency.

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