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FORMULATION, DEVELOPMENT AND CHARACTERIZATION OF MOUTH DISSOLVING CINNARIZINE TABLETS

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ABSTRACT

Aim: *The aim of current study is to develop mouth dissolving tablets of cinnarizine by direct compression method employing superdisintegrants. Computer-aided optimization technique, using a central composite design (CCD), was employed to investigate the effect of three independent variables i.e., amount of lepidium sativum seed mucilage, amount of sodium starch glycolate and amount of their mixture in superdisintegrant addition method on the various response variables viz., disintegration time, wetting time, water absorption ratio and cumulative percentage drug release (12 min).* ***Study Design:*** *Cinnarizine mouth dissolving tablets were prepared by direct compression method through wet granulation using PVP K-30 in isopropyl alcohol (10% w/w) as a binder. Microcrystalline cellulose was used as directly compressible material, mannitol as diluent and magnesium stearate as lubricant. All ingredients were mixed together and sufficient quantity of alcoholic solution of PVP was added and mixed to form a coherent mass. Wet mass was granulated using sieve no. 12. Granules were re-granulated and finally compressed into tablets by using 5mm punch using fluid pack 8 station mini rotary tablet punching machine (4D+4B type)[1-2]. Mouth dissolving tablets of cinnarizine were formulated using different concentrations of superdisintegrants (Lepidium sativum seed mucilage as natural and Sodium starch glycolate as synthetic) and also by using their different combinations. Face centered central composite design (FCCCD) was used to optimize the effective concentration of superdisintegrants. The tablets were evaluated for Weight variation[7-10], Thickness, Hardness, Friability, Disintegration time, Wetting time, Drug content, Water absorption time, in-vitro dissolution for drug release studies and mathematical modeling with drug release kinetics of optimized batches.*

KEY WORDS

Central composite design (CCD), Face centered central composite design (FCCCD), super disintegrants and Cinnarizine.

INTRODUCTION

Oral Drug Delivery Systems

Drugs can be administered via many different routes to produce systemic pharmacological effects. Among all the dosage form that are administered orally, Tablets are popular because of ease of administration, accurate dosing, self-medication, pain avoidance and most importantly the patient compliance[3-4].

Mouth Dissolving Tablets

Mouth dissolving drug delivery systems are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations, and at the same time, offer added advantages over both the traditional dosage forms. They provide the convenience of a tablet formulation and also allow the ease of swallowing provided by a liquid formulation[1]. These dosage forms rapidly disintegrate and/or dissolve to

release the drug as soon as they come in contact with saliva. The faster the drug into solution, quicker the absorption and onset of clinical effects. A fraction of pregastric drug absorption may bypass the digestive system and metabolism by the stomach acids and enzymes. The concept of Mouth dissolving drug delivery systems emerged with an objective to improve patient's compliance. This segment of formulation is especially designed for dysphagic, geriatric, pediatric, bed-ridden, travelling and psychotic patients who are unable to swallow or refuse to swallow conventional oral formulations[5-6].

MATERIALS AND METHODS

PREPARATION OF MOUTH DISSOLVING TABLETS

Materials Used

Cinnarizine was obtained from Wallace pharmaceuticals Pvt. Ltd., Goa, *Lepidium Sativum* from Kurukshetra Local Market, Sodium Starch Glycolate from Ranbaxy Laboratories Pvt. Ltd., Gurgaon, Microcrystalline Cellulose from Maple Biotech Pvt. Ltd., Pune, Mannitol from RFCL Ltd., New Delhi and Magnesium Stearate, Talc, Sodium Saccharin, Potassium Dihydrogen Phosphate, Sodium Hydroxide, Hydrochloric Acid, Isopropyl Alcohol, PVP K-30 from S.D. Fine-Chem Ltd., Mumbai.

Direct compression method[5]:

Cinnarizine mouth dissolving tablets were prepared by direct compression method through wet granulation using PVP K-30 in isopropyl alcohol (10% w/w) as a binder. A total number of thirteen formulations were prepared as per the standard experimental design protocol. In these formulations, microcrystalline cellulose was used as directly compressible material, mannitol as diluent and magnesium stearate as lubricant. All ingredients were weighed accurately and passed through 60-mesh sieve separately and collected. They were mixed together and sufficient quantity of alcoholic solution of PVP was added and mixed to form a coherent mass. Wet mass was granulated using sieve no. 12.

Granules were re-granulated after drying in hot air oven at 60°C through sieve no. 16 and evaluated for granular properties. Dried granules were mixed with magnesium stearate and talc and finally compressed into tablets by using 5mm punch using fluid pack 8 station mini rotary tablet punching machine (4D+4B type)[1-2].

In this approach, mouth dissolving tablets of cinnarizine were formulated using different concentrations of superdisintegrants (*Lepidium sativum* seed mucilage as natural and Sodium starch glycolate as synthetic) and also by using their different combinations.

Experimental design for formulations of Cinnarizine

Two independent variables, (i) the amount of Mucilage (X_1), microcrystalline cellulose (MCC) (X_2), SSG (X_1) and MCC(X_2) and Mucilage (X_1), and SSG (X_2) were studied for all three types of formulations at 3 levels each. The central points (0, 0) were studied in quintuplicate. All other formulation and processing variables were kept invariant throughout the study. Disintegration time (DT), wetting time (WT), water absorption ratio (WAR) and cumulative % drug release (%CDR) were taken as the response variables. Tables 1(a), 1(b) and 1 (c) and 1 (d) summarize an account of the 13 experimental runs studied, their factor combinations and the translation of the coded levels to the experimental units employed during the study.

Table 1(a): Factor combination according to CCD influencing DT, WT, WAR, %CDR

Batch code	Coded factor levels	
	X_1	X_2
A_1	-1	-1
A_2	-1	0
A_3	-1	+1
A_4	0	-1
A_5	0	0
A_6	0	+1
A_7	+1	-1
A_8	+1	0
A_9	+1	+1
A_{10}	0	0
A_{11}	0	0
A_{12}	0	0
A_{13}	0	0

Table 1(b): The amount of factors selected for optimization in different levels

Coded level	-1	0	+1
X_1: Mucilage (mg)	3.00	7.50	12.00
X_2: MCC (mg)	95.00	98.50	102.00

Table 1(c): The amount of factors selected for optimization in different levels

Coded level	-1	0	+1
X_1: SSG (mg)	3.00	7.50	12.00
X_2: MCC (mg)	95.00	98.50	102.00

Table 1 (d): The amount of factors selected for optimization in different levels

Coded level	-1	0	+1
X_1: Mucilage (mg)	1.50	3.75	6.00
X_2: SSG (mg)	1.50	3.75	6.00

General appearance

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape were found to be within the acceptable limit of pharmacopeia.

Other parameters like Weight variation, Thickness, Hardness, Friability, Disintegration time, Wetting time, Drug content, Water absorption time were found within acceptable limits.

Evaluation of tablets of optimized batch from Pool A

Table 2: Evaluation parameters of tablets of optimized batch

Batch code	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	DT (sec)	WT (sec)	WAR (%)	%CDR
A_9	150.6 ± 0.41	3.4 ± 0.20	0.134	3.4 ± 0.05	61.22	45.01	96.24	98.38

Table 2(b): *In vitro* dissolution data of final optimized batch

Time (min)	0	2	4	6	8	10	12	15	20	25	30
%CDR	0	57.63 ± 1.10	68.89 ± 0.69	78.58 ± 0.54	87.44 ± 1.02	94.36 ± 0.58	98.38 ± 0.27	98.42 ± 0.34	98.89 ± 0.86	99.23 ± 0.29	99.81 ± 0.57

Table 3(a): Evaluation parameters of tablets of optimized batch from Pool B

Batch code	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	DT (sec)	WT (sec)	WAR (%)	%CDR
B_9	149.2 ± 0.41	3.5 ± 0.20	0.142	3.12 ± 0.05	70.39	49.65	91.85	96.82

Table 3(b): *In vitro* dissolution data of final optimized batch

Time (min)	0	2	4	6	8	10	12	15	20	25	30
%CDR	0	52.93 ± 1.05	64.66 ± 0.98	75.45 ± 1.02	86.78 ± 0.56	92.31 ± 0.47	96.82 ± 0.85	96.82 ± 0.85	96.82 ± 0.85	96.82 ± 0.85	96.82 ± 0.85

Table 4(a): Evaluation parameters of tablets of optimized batch from Pool C

Batch code	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	DT (sec)	WT (sec)	WAR (%)	%CDR
C_9	150.8 ± 0.41	3.2 ± 0.20	0.125	3.0 ± 0.05	60.21	47.02	94.48	96.67

Table 4(b): *In vitro* dissolution data of final optimized batch

Time (min)	0	2	4	6	8	10	12	15	20	25	30
%CDR	0	53.21 ± 0.51	65.43 ± 0.78	76.19 ± 0.24	85.54 ± 1.35	92.30 ± 1.64	96.67 ± 0.31	97.85 ± 0.51	98.39 ± 0.36	98.95 ± 0.21	99.89 ± 0.11

Table 5: Drug content for optimized batches

Batch code	Absorbance at 272 nm	Drug content (%) ±SD
	Direct compression method	
A_9	0.770, 0.768, 0.770	99.98 ± 0.15
B_9	0.764, 0.763, 0.766	99.85 ± 0.21
C_9	0.762, 0.764, 0.762	99.31 ± 0.18

Kinetic study of drug release

Data obtained from *in-vitro* dissolution studies were fitted in different models viz. zero order model, first order model, Higuchi model, Hixson-Crowell model and Korsmeyer peppas model. Results are shown below:

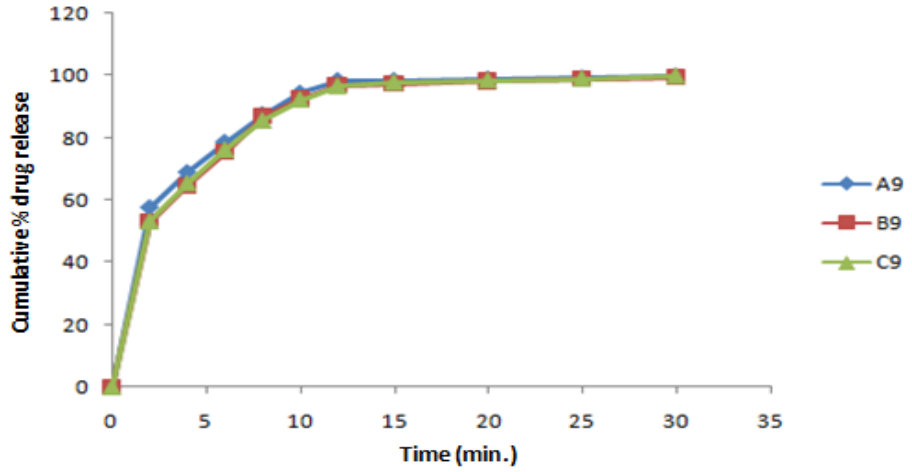

Fig. 1: *In-vitro* release data of A_9, B_9 and C_9 formulations: zero order kinetics.

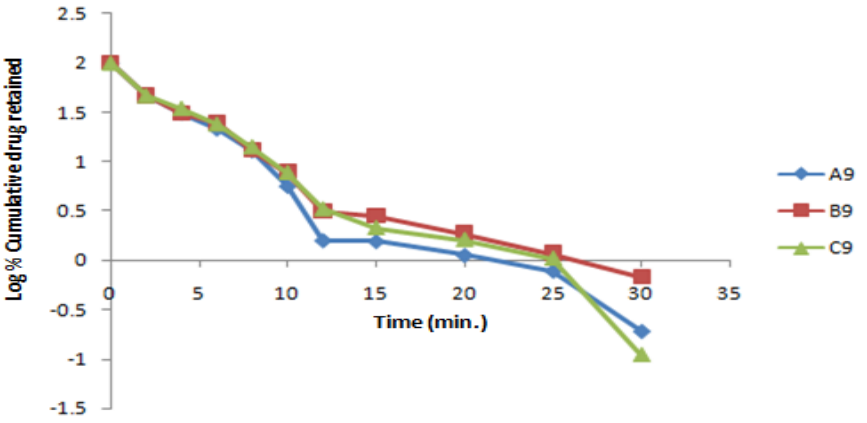

Fig. 2: *In-vitro* release data of A, B and C formulations: Zero order kinetics

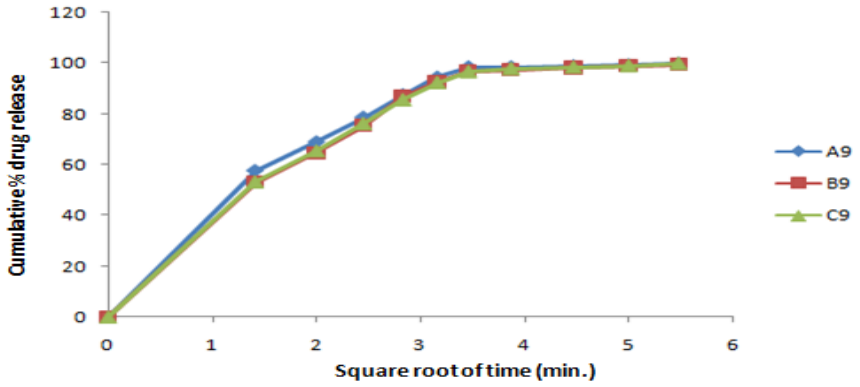

Fig. 3: *In-vitro* release data of A_9, B_9 and C_9 formulations: Higuchi kinetics.

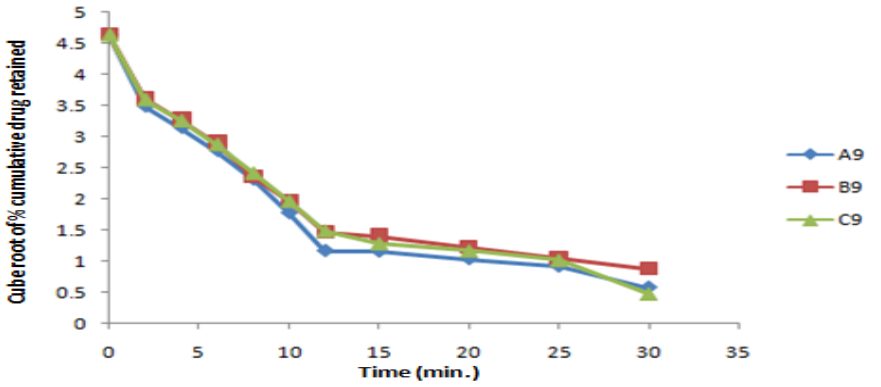

Fig. 4: *In-vitro* release data of A_9, B_9 and C_9 formulations: Hixson-Crowell kinetics.

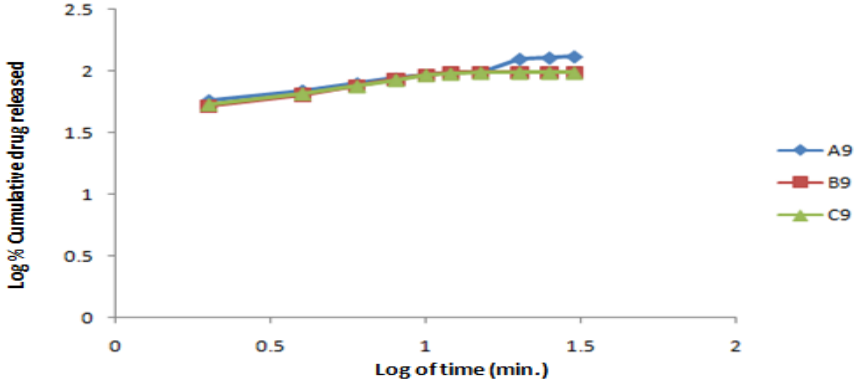

Fig. 5: *In-vitro* release data of A_9, B_9 and C_9 formulations: Korsmeyer peppas model.

Table 6: Value of R^2 obtained from different kinetics models

Kinetic models	Value of R^2		
	Direct compression method		
Zero order model	0.490	0.524	0.528
First order model	0.921	**0.956**	**0.927**
Higuchi model	0.774	0.802	0.806
Hixson-Crowell model	0.797	0.804	0.847
Korsmeyer peppas model	**0.977**	0.859	0.879
Best suited model	**Korsmeyer peppas model**	**First order model**	**First order model**

In 0 sec **In 10 sec**

Fig. 6: Diagram showing various steps involved in the disintegration of the tablet

SUMMARY AND CONCLUSION

The objective of present study was to formulate, evaluate and optimize mouth dissolving tablets of cinnarizine whose optimization was carried out using central composite design – response surface methodology for optimizing the components of tablets for various parameters like disintegration time, wetting time, water absorption ratio and in-vitro drug release studies[1-2].

The disintegration times of all the formulations were within official requirements i.e. less than 180 sec. The disintegration time ranged from 61 to 127 sec and from 56 to 96 sec for direct compression and sublimation method batches respectively. Wetting time was found from 45 to 89 sec and from 17 to 62 sec for direct compression and sublimation method batches respectively. This showed good correlation between disintegration time in the oral cavity and wetting time for all formulations.

In direct compression method, the batches A_9, B_9 and C_9 were found optimized according to the face centered central composite design. Out of these batches, batch A_9 showed least disintegration time (61 sec), least wetting time (45 sec), maximum water absorption ratio (96.24%) and maximum *in-vitro* drug release 99.81% in 30 min. From the results, it was concluded that natural superdisintegrant *lepidium sativum* seed mucilage powder showed better disintegrating property than the most widely used synthetic superdisintegrant sodium starch glycolate in the formulations of MDTs and its optimized level was 8% w/w in tablet formulations.

The optimized batches were further subjected to kinetic modeling studies. In kinetic modeling studies, on the basis of R^2 values obtained for different models, it was concluded that batch A_9 showed korsmeyer peppas model (R^2 = 0.977) whereas, batches B_9 and C_9 showed first order model (R^2 = 0.956, 0.927 for B_9 and C_9 respectively) as drug release model.

It is noteworthy to envisage that this natural super disintegrant could be considered for developing a future disintegrating system for MDTs.

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