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Research Article

Influence of Formulation Variables and Processing Techniques on Drug Release from Carbopol-971 based Matrix Tablets of Cinnarizine and Nimodipine.

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ABSTRACT
The matrix tablets of cinnarizine and nimodipine were prepared with varying ratio of Carbopol- 971P and co-excipients of varying hydrophilicity (i.e. dicalcium phosphate and spray dried lactose) by direct compression and wet granulation using alcoholic mucilage. The prepared tablets were evaluated for weight variation, hardness and friability. The influence of concentration of the matrix forming material and co-excipients on the release rate of the drug was studied. The release rate of Cinnarizine (more soluble drug) from tablets followed diffusion controlled mechanism whereas for nimodipine (less soluble drug), the drug release followed case-II or super case- II transport mechanism based on Korsmeyer- Peppas equation. The results indicated that the drug release from matrix tablets was increases with increase in hydrophilicity of drug and co-excipients. The release of drug also increased with thermal treatment and decreasing polymer concentration.

Key Words: Matrix tablet, Carbopol 971P, Co- excipient, Cinnarizine, Nimodipine.

INTRODUCTION

Embedding a drug within an insoluble matrix provides a convenient means of controlling the drug release. In such a system, the drug release proceeds by penetration of the dissolution medium into the porous matrix to dissolve the drug, followed by diffusion/ leaching of the dissolved drug molecules out of the matrix[1]. Recently, carbomer resins have enjoyed tremendous success in controlled release matrix tablets. These polymers offer a choice of release profiles, compatibility with a variety of active ingredients and other excipients, desirable tablet characteristics and convenience of using standard manufacturing methods and equipments. Carbopol resins are ideal for direct compression processes, as they get compressed very well, and also have very strong binding characteristics[2,3]. Carbopol 971P is new oral pharmaceutical grade polymer which is polymerized in ethyl acetate. It readily hydrates, absorb water and swell quickly. The Carbomer Homopolymer Monograph became official on January 1, 2006 in USP 29-NF 24 and included a delayed implementation date up to January 1, 2011. Prior to January 1, 2011, the current practice of labeling products with the Carbomer 941 name may be continued. However this product is also official in European Pharmacopeia (Ph. Eur.) monograph for Carbomers and Japanese Pharmaceutical Excipients (JPE) monograph for Carboxyvinyl Polymer. Its hydrophilic nature and highly cross-linked structure renders them a suitable candidate for use in controlled release drug delivery systems[4]. The drug release from the Carbopol matrix tablets can be explained as follows. In the dry state, the drug is trapped in glassy core and forms a gelatinous layer upon hydration. The hydrogels are not entangled chains of polymer but discrete microgels made up of many polymer particles. When the hydrogel is fully hydrated, the osmotic pressure, from within the networks break up the structure, by sloughing off discrete pieces of hydrogels. The gel layer formed around the tablet core also acts like a rate controlling membrane[5]. Many authors have studied the release from matrix tablet and evaluated kinetics of drug release from the tablet containing carbopol as matrix forming agent[2,4,6,7,8]. Few authors have studied the effect of thermal treatment on drug release from matrix tablets[1].

Cinnarizine is used in the treatment of vertigo, tinnitus, meniere's disease, loss of memory and motion sickness. It also improves blood flow to labyrinth and brain stem and thus is useful in cerebrovascular and peripheral disorder[9,10]. Nimodipine, a dihydropyridine calcium channel blocker is used in the treatment of senile dementia and in the prophylaxis of the vascular hemierania[11]. The objective of the present study was to formulate matrix tablet and to investigate the influence of nature of diluents and polymer concentration on the drug release (Cinnarizine and Nimodipine) from Carbopol 971P matrices. The study also included the influence of thermal treatment on drug release.

MATERIALS AND METHODS

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Table-1 :**Composition of different formulations (D = Direct Compression, SD = Compression after Thermal treatment)**

Ingredients (mg)	D1 / SD1	D2 / SD2	D3 / SD3	D4 / SD4	D5 / SD5	D6 / SD6	D7	D8
Cinnarizine	75	75	75	75	--	--	--	--
Nimodipine	--	--	--	--	60	60	60	60
Carbopol-971	75	75	37.5	37.5	60	60	30	30
Dicalcium Phosphate	75	--	112.5	--	60	--	90	--
Spray Dried Lactose	--	75	--	112.5		60	--	90
Mg-Stearate	02	02	02	02	02	02	02	02
Total weight	227	227	227	227	182	182	182	182

Cinnarizine and Nimodipine were obtained as gift sample from Novachem SA, Switzerland (through Geno Pharmaceuticals, Goa, India) and US Vitamins Limited, Mumbai, respectively. Carbopol® 971 was gifted by B. F. Goodrich Co., USA. Dicalcium phosphate (DCP) and spray dried lactose were procured from Vardhman Healthcare, Ambala, India. All other chemicals used were of analytical grade.

Preparation of Matrix Tablets

All the ingredients (Table-1) were screened through a sieve (# 80), mixed together for 30 minutes in a double cone blender and again passed through a sieve (# 80). The mixed blend was compressed into tablets using a single punch R&D tablet-punching machine producing biconvex tablets of 8 mm diameter weighing 227.0 mg for cinnarizine tablets and 182 mg for nimodipine tablets. A total of 8 batches of tablets (D1-D8) were prepared containing 50 tablets in each batch.

Thermal treatment of powder mixture

The powder mixtures excluding magnesium stearate were kept at 80^0C in an oven for 24 hrs. It was cooled to room temperature, passed through a sieve (# 80) after mixing magnesium stearate and compressed into tablet as described earlier. A total of 6 batches of tablets were prepared

Table-2: Various evaluation parameters of matrix tablets prepared with Carbopol-971

Parameter	D1	D2	D3	D4	D5	D6	D7	D8
Weight[a](mg)	226.4±3.7	225.8±3.8	229.8±4.6	225.7±5.8	183.3±5.7	185.8±3.6	178.3±4.5	184.2±3.2
Hardness[a] (kg)	7.9±0.5	7.6±0.9	5.6±0.9	5.3±0.7	6.8±0.7	6.9±0.7	6.4±0.5	6.5±0.7
Friability[b](%)	0.26	0.29	0.42	0.39	0.28	0.33	0.43	0.38
DR_{2h} (%)	7.28±0.73	11.78±1.57	11.30±1.02	12.89±1.24	1.98±0.09	1.99±0.09	8.14±0.23	8.79±0.44
DR_{8h} (%)	24.28±2.24	34.34±4.36	29.80±3.23	41.70 ±7.46	4.36±0.19	6.78±1.09	45.39±4.78	50.37±5.93
$t_{25\%}$ (hrs)	7.8	5.0	6.1	4.4	289.7	33.0	4.8	4.3
$t_{50\%}$ (hrs)	16.3	12.4	16.5	10.8	1154.5	66.6	9.3	8.3
$t_{90\%}$ (hrs)	30.5	26.6	38.1	23.3	3734.5	120.2	16.6	14.7
Best Fit Model	Korsmeyer -Peppas	Korsmeyer -Peppas	Korsmeyer –Peppas	Korsmeyer –Peppas	Higuchi Matrix	Zero order	Zero Order	Zero Order
R	0.9981	0.9980	0.9962	0.9987	0.9919	0.9780	0.9935	0.9952
K*	3.5983	7.2263	7.0084	7.9911	1.3597	1.5411	5.0786	5.8376
n*	0.9422	0.7689	0.7013	0.7695	0.5283	0.5915	0.9798	0.9785

* The value of K and n are shown according to Korsmeyer -Peppas equation., a: n = 10, b: n = 20

Table-3 Various evaluation parameters for matrix tablets prepared with Carbopol-971 after thermal treatment

Parameter	SD1	SD2	SD3	SD4	SD5	SD6
Weight[a](mg)	226.4±4.7	227.8±5.8	225.8±4.6	227.7±6.8	183.3±5.5	185.8±4.6
Hardness[a] (kg)	5.1±0.4	5.2±0.9	5.7±0.7	5.1±0.3	5.8±0.6	5.5±0.7
Friability[b](%)	0.56	0.68	0.69	0.77	0.44	0.55
DR_{2h} (%)	19.96±1.58	10.78±1.12	11.50±1.45	16.47±1.23	3.18±0.16	2.09±0.47
DR_{8h} (%)	51.92±5.15	51.49±5.64	33.63±4.68	46.02±4.44	5.32±1.45	11.34±2.44
$T_{25\%}$ (hrs)	2.8	3.9	5.4	4.1	190.9	20.2
$T_{50\%}$ (hrs)	7.6	7.8	13.7	9.4	769.3	40.2
$T_{90\%}$ (hrs)	16.6	14.0	30.0	19.0	2500.5	72.2
Best Fit Model	Korsmeyer - Peppas	Zero Order	Korsmeyer – Peppas	Korsmeyer - Peppas	Higuchi Matrix	Zero Order
R	0.9967	0.9984	0.9989	0.9937	0.9865	0.9775
K*	10.6287	6.8536	7.0142	7.7209	2.0503	1.5017
n*	0.7844	0.9410	0.7504	0.8347	0.4453	0.8265

* The value of K and n are shown according to Korsmeyer -Peppas equation., a: n = 10, b: n = 20

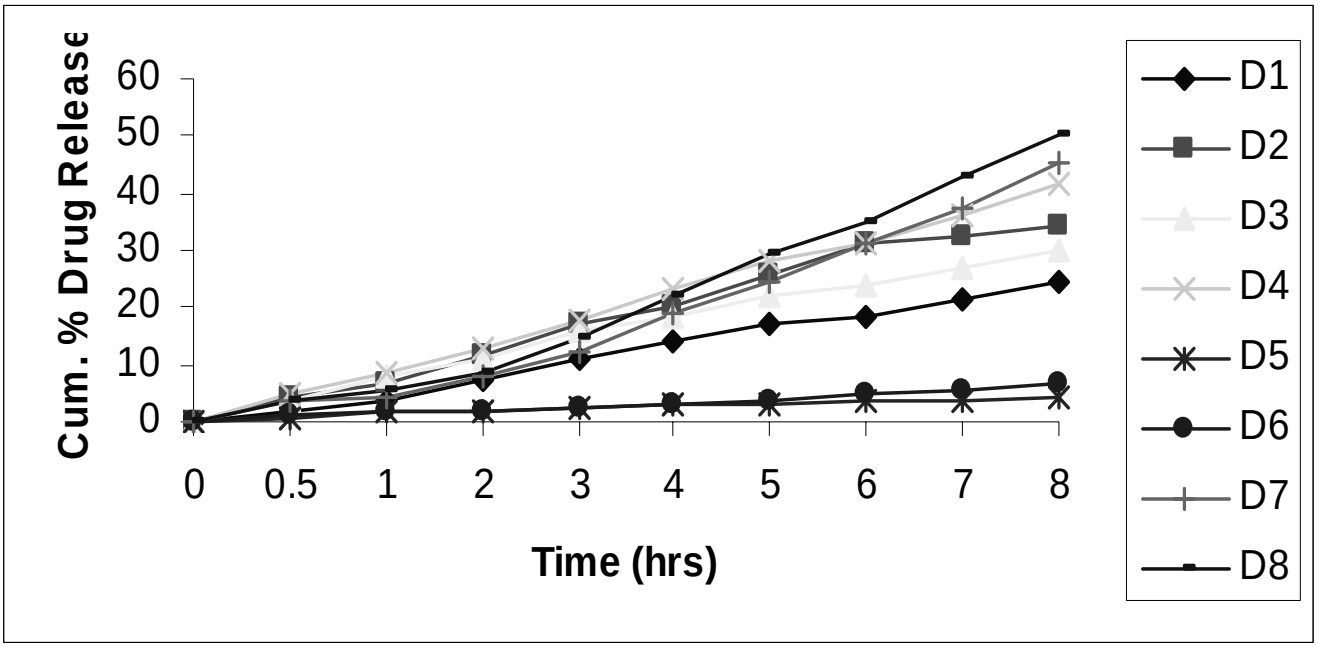

Fig 1: drug release from matrix tablets prepared with carbopol-971

containing 50 tablets in each batch. (Table-1, Formulations SD1-SD6)

Uniformity of weight, Hardness and friability

For uniformity of weight, 10 tablets from each batch were weighed individually and average weight and deviation from average were determined. The hardness of the tablets was determined using Monsanto hardness tester, whereas, the friability of the prepared tablets was determined using Roche friabilator at 25 rpm for 4 minutes after placing twenty tablets and percent loss in weight was calculated.

***In Vitro* Dissolution Studies**

In vitro dissolution studies of all the fabricated tablets were carried out using USP-XXIV dissolution rate test apparatus (rotating paddle) at 50 rpm at 37 ± 0.5^0 C for 8 hrs. Dissolution medium for cinnarizine tablet and nimodipine tablet were 900 ml of 0.1 N HCl and distilled water containing 0.2 % w/v sodium lauryl sulphate (SLS) respectively. Nimodipine is practically insoluble in water therefore, for *in vitro* drug release studies 0.2 % SLS solution was used as dissolution medium to maintain the sink condition[12]. An aliquot of 10 ml were withdrawn at various time intervals and equal volume of dissolution medium, maintained at the same temperature, was added to the dissolution vessel to maintain the constant volume of dissolution medium. The samples were diluted suitably and analyzed using UV-VIS Spectrophotometer (Systronics-108) at 254 nm (for cinnarizine) and 240 nm (for nimodipine) against suitable blank. The drug release

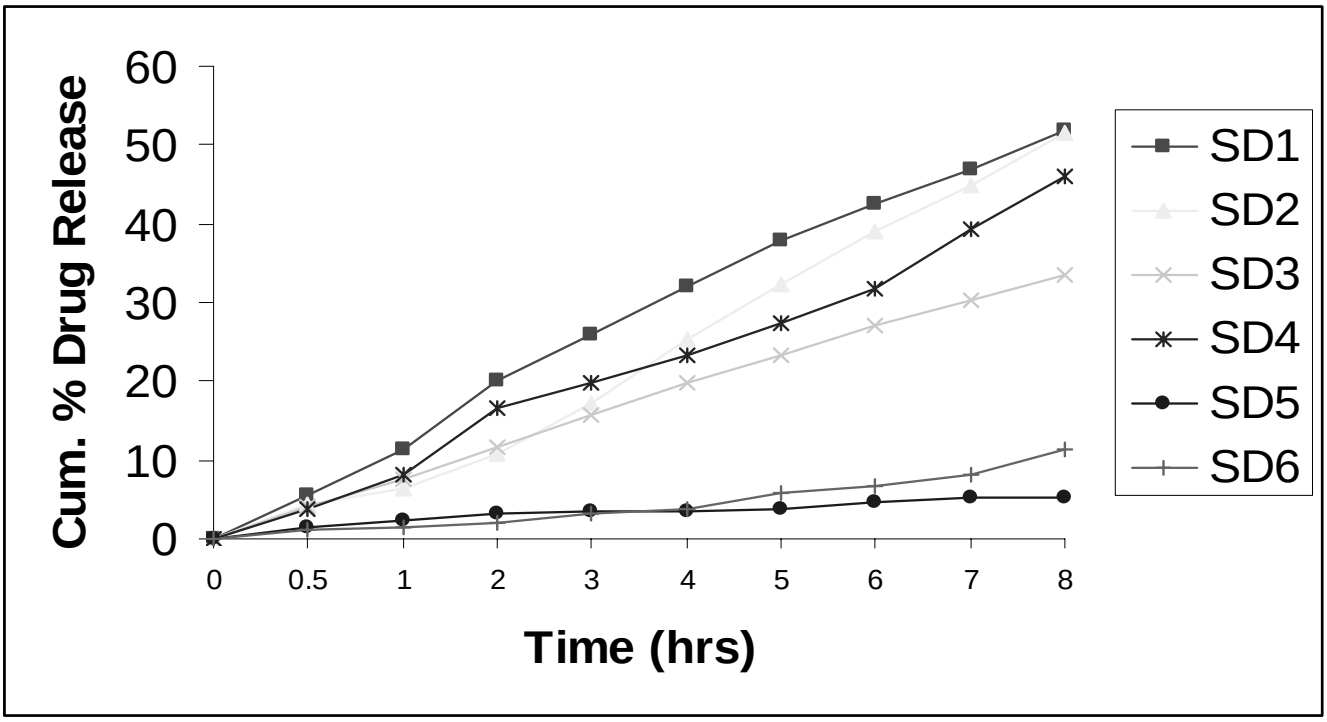

Fig 2: Drug release from matrix tablets prepared with Carbopol-971 after thermal treatment

parameters i.e. drug release in 2h (DR2h), 8 h (DR8h), time taken for 25% drug release (t25%) and 50% drug release (t50%), are calculated and are shown in Table 2 for the tablets made by direct compression. The dissolution data for tablets prepared after thermal treatment of powder are shown in Table 3.

Model of drug release

The drug release profile was subjected to different models of drug release and best-fit model was selected on the basis of correlation coefficient (r). The values of "K" and "n" are determined for Korsmeyer –Peppas equation. The value of n in Korsmeyer–Peppas equation is used to indicate different release mechanisms. The value of n = 0.5 indicates Fickian Diffusion (Higuchi Matrix), 0.5<n<1 indicates Anomalous Transport, n = 1 indicates Case-II Transport (Zero Order Release) and n>1 indicates Super Case-II transport[13,14].

RESULTS AND DISCUSSION

The compositions of various batches of tablet formulations prepared by direct compression with and without thermal treatment are shown in Table-1. Weight variation, hardness and friability of the prepared matrix tablets were observed to be well within official limit (Table-2 and 3). Tablet hardness was higher with higher carbopol content and less for the tablets prepared after thermal treatment of powder mixture, which may be attributed to decrease in binding/ gelling property. Friability was higher with tablets having lesser hardness particularly with the tablets made after thermal treatment of powder. Although the compression force is closely related to the porosity of the tablet, some authors have reported that the porosity of hydrated matrix is independent of the initial porosity and the compression force has little influence on drug release[5,15].

Influence of nature of the drug and Drug / Polymer Ratio

In this study, two drugs namely Cinnarizine (more soluble) and Nimodipine (less soluble) were used. The drug release from matrix tablets of cinnarizine, followed Korsmeyer-Peppas model indicating anomalous transport with diffusion of drug from the swelled hydrogel as the main mechanism with value of "n" in Korsmeyer -Peppas equation lying between 0.7013 and 0.9422 for D1 to D4 (Table-2). Similar results were reported by Tapia-Albarran et al[16], where the value of "n" ranges from 0.5 to 1. With tablets containing nimodipine (low soluble drug) at higher concentration of carbopol, the drug release was 4.36 and 6.78 % only in 8 hrs. When the concentration of carbopol was decreased from 33 % to 16.5 % there was release of 45.39 and 50.37 % respectively (D7 and D8; Table-2) with the value of "n" in Korsmeyer -Peppas equation was 0.9798 and 0.9785 respectively indicating Case-II transport (Zero order release). Moreover, drug release was found to be higher with decreased polymer content in the tablet, indicated by higher values of DR2h and DR8h by the formulations D3, D4, D7 and D8 in comparison to the formulations D1, D2, D5 and D6 respectively (Table-2).

Influence of Diluents on drug release

It was observed that the drug release was higher with spray dried lactose (organic diluent) than dicalcium phosphate (inorganic diluent). The higher hydrophilicity of the organic diluent than the inorganic counterpart, results in faster movement of solvent front i.e. easier penetration of dissolution medium into the tablet matrix resulting in faster drug release. The time taken for 25% drug release ($t_{25\%}$) in formulations containing spray dried lactose (D2, D4, D6 and D8) was observed to be 5.0, 4.4, 33.0 and 4.3 hrs respectively in comparison to the formulations containing dicalcium phosphate D1, D3, D5 and D7 ($t_{25\%}$ = 7.8, 6.1, 289.7 and 4.8 hrs respectively) as shown in Table-2. With matrix tablets containing Cinnarizine the DR8h was 34.34 and 41.70 for tablets containing spray dried lactose whereas it was 24.28 and 29.80 for tablets containing dicalcium phosphate indicating higher drug release with organic diluent and the best fit model for drug release was Korsmeyer–Peppas model. With tablets of nimodipine containing spray dried lactose, the best fit model for drug release was Zero order though the drug release mechanism was anomalous transport with all the tablets.

Effect of Thermal treatment

It was observed that the drug release from the matrix tablets was higher with thermal treatment of powder. The drug release mechanism was anomalous transport (value of "n" observed between 0.5 to 1), except formulation D5 where the drug release followed Fickian diffusion (n=0.4453). The best fit models based on highest value of regression coefficient are shown in table 3. The rate limiting factor was found to be the solubility and hydrophilicity of drug. It seems that thermal exposure resulted into loss of gelling property as indicated by lower hardness of these tablets (Table 3).

CONCLUSION

This study provided an insight into the release mechanism of Cinnarizine and Nimodipine from the carbopol matrix tablets and the significance of nature of the diluent. The Cinnarizine matrix tablets followed predominantly anomalous transport whereas, the drug release kinetics for nimodipine matrix tablet varied from anomalous transport to zero order release.

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