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Influence of Drug Solubility, Drug Polymer Ratio, Nature of Co-excipients and Thermal Treatment on Drug Release from Carbopol 974P Matrix Tablets

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Abstract

In this study, matrix tablets of cinnarizine and nimodipine were prepared with Carbopol- 974 at different drug to polymer ratio along with co-excipients of varying hydrophilicity i.e. dicalcium phosphate and spray dried lactose. At higher polymer concentration, the drug release was slow and followed super case II transport mechanism. At lower concentration of carbopol, the diffusion mechanism was anomalous transport as indicated by lower value of n for both the drugs. Nature of excipient was observed to be important where hydrophilic excipient favored drug release with respect to the inorganic less hydrophilic counterpart.

Keywords: Matrix tablet, Carbopol 974P, co-excipient, cinnarizine, nimodipine.

Introduction

Controlled delivery of bioactive agents is a major focus of pharmaceutical research since multiple dosing regimens often present problems with patient compliance, toxicity and therapeutic index (Sood *et al.*, 2003).

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Polymeric drug carrier systems have been widely studied to sustain, modify or target drug delivery (Young *et al.*, 2005). Matrix systems containing hydrophilic polymers have been widely studied since drug release from these matrices is controlled by a combination of polymer swelling, erosion and diffusion through the hydrated gel (Di Colo *et al.*, 2001). One of the most interesting and widely studied swellable systems in controlled drug delivery involves the Carbopol or Carbomer group of polymers (Goskonda *et al.*, 1998). 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 compress very well, and also have very strong binding characteristics (B. F. Goodrich Bulletin 1994; Khan *et al.*, 1998). Carbopol 974P is the oral pharmaceutical grade of the carbomers. It is a synthetic high molecular weight crosslinked polymer of acrylic acid, which is polymerized in ethyl acetate and is slightly treated with (1-3%) potassium. It readily hydrates, absorbs water and swells. Their hydrophilic nature and highly cross linked structure render them more suitable potential candidate for use in controlled release drug delivery systems (Jivraj *et al.*, 2000). The drug release from the Carbopol matrix tablets has been explained by Khan et al, 1999 as follows. In the dry state, the drug is trapped in glassy core and forms gelatinous layer upon hydration. When the hydrogel is fully hydrated, osmotic pressure, from within the networks break up the structure, essentially by sloughing off discrete pieces of hydrogels. The gel layer formed around the tablet core also acts almost like the rate controlling membrane. Many authors have studied the release from matrix tablet and evaluated kinetics of drug release from the tablet containing carbopol as matrix forming agent (Marcos *et al.*, 1991; Durrani *et al.*, 1994; Huang *et al.*, 1995; Goskonda *et al.*, 1998; Khan *et al.* 1998; Khan *et al.* 1999; Genc *et al.*, 1999). Few authors have studied the effect of thermal treatment on drug release from matrix tablets (Billa *et al.*, 1998).

Cinnarizine, used in vertigo, tinnitus, meniere's disease, loss of memory and motion sickness, also improves blood flow to labyrinth and brain stem and thus is useful in

cerebrovascular and peripheral disorder (Godfraind *et al.*, 1982). Nimodipine is a dihydropyridine calcium channel blocker, used in the treatment of senile dementia and in the prophylaxis of the vascular hemierania (Manhold, 1985). The objective of the present study was to formulate and investigate the influence of nature of diluents and carbopol concentration on the release of cinnarizine (more soluble drug) and nimodipine (less soluble drug) from matrix tablet and the influence of thermal treatment on drug release profile and best-fit model of drug release kinetics.

Materials and Methods

Cinnarizine and nimodipine were obtained as gift sample from Novachem SA, Switzerland (through Geno Pharmaceuticals, Goa, India) and US Vitamins Limited, Mumbai, respectively. Carbopol® 974 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) after screening through a sieve (# 80 mesh), were mixed geometrically with mortar and pestle and then mixed together for 30 minutes in a double cone blender and then passed through a sieve (# 80 mesh). The mixed blend was compressed using a single punch R&D tablet-punching machine producing biconvex tablets of 8 mm diameter weighing 227.0 mg for cinnarizine tablets and 182.0 mg for nimodipine tablets as shown in Table 1. A total of 8 batches of tablets (D1-D8) were made containing 50 tablets in each batch.

Effect of thermal exposure: The powder mixture except magnesium stearate (Table 1, Formulation SD) was mixed geometrically with mortar and pestle and then kept at 80^0C in an oven for 24 hrs and thereafter cooled to room temperature. The mixture after mixing magnesium stearate was passed through a sieve (# 80 mesh) and compressed using single punch R&D tablet punching machine as described earlier. A total of 6 batches of tablets (SD1-SD6) were made containing 50 tablets in each batch.

Uniformity of weight, Hardness and friability: For uniformity of weight, 10 tablets from each batch were weighed individually and their average weight and deviation from average were determined. The hardness of the tablets was determined using Monsanto hardness tester. The friability of the prepared tablets was determined using Roche friabilator at 25 rpm for 4 minutes (100 revolutions) after placing twenty tablets and recording percent loss in weight.

In Vitro Dissolution Studies: In vitro dissolution studies of all the tablets were carried out using USP-XXIV dissolution rate test apparatus (rotating paddle apparatus) at 50 rpm maintaining the temperature of dissolution medium at $37\pm0.5^{0}C$ for 8 hrs. Dissolution medium for cinnarizine tablet and nimodipine tablet were 900 ml of 0.1 N HCl, 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 is used as dissolution medium to maintain the sink condition (Babu *et al.*, 2002). An aliquot of 10 ml were withdrawn at various time intervals and equal volume of dissolution medium was added 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. Drug release in 2h (DR2h), 8 h (DR8h), time taken for 25% drug release ($t_{25\%}$), 50% drug release ($t_{50\%}$) and 90% drug release ($t_{90\%}$), are shown in Table 2 for the tablets made by direct compression. The dissolution data for tablets prepared from sintered granules (After Thermal Treatment) are shown in Table 3. Wherever required $t_{25\%}$, $t_{50\%}$ and $t_{90\%}$ were predicted in accordance with the best-fit model.

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) and the values of "K" and "n" are determined for Korsmeyer –Peppas equation. The value of n (release exponent) 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, 1 indicates Case-II

Transport (Zero Order Release) and n>1 indicates Super Case-II transport (Korsmeyer *et al.*, 1983; Costa *et al.*, 2001).

Results and Discussion

The compositions of various formulations prepared by direct compression and thermal treatment are shown in Table 1.

Table 1. Composition of different formulations

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-974P	75	75	37.5	37.5	60	60	30	30
Dicalcium Phosphate	75	--	112.5	--	60	--	90	--
Spray Dried Lact	--	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

(D = Direct Compression, SD = Compression after Thermal treatment)

Weight variation, Hardness and friability of the prepared batches of tablets were observed to be well within official limit (Tables 2 and 3). Tablet hardness was higher with matrix tablets where carbopol was more and the tablet hardness was less with tablets prepared after thermal exposure of mixture, which may be attributed to loss in gelling property. Friability was higher with tablets having lesser hardness. Marcos et al. had reported that the compression force had no effect on drug release from carbomer matrices (1991).

Influence of nature of drug and influence of drug / polymer ratio: In this study, two drugs, cinnarizine (more soluble) and nimodipine (less soluble) were used. It was observed that the drug release from matrix tablets made with cinnarizine (more

soluble drug) was slower with higher percentage of carbomer and the value of "n" in Korsmeyer - Peppas equation was 1.0165 and 1.0284 for D1 and D2 respectively which decreased upon decreased percentage of carbopol to 0.7566 and 0.8459 respectively with formulations D3 and D4 respectively. Similar effects were observed with formulations containing nimodipine where the value of "n" in Korsmeyer - Peppas equation was observed to be 1.3958, 1.2122, 0.6714 and 0.6104 for formulation D5, D6, D7 and D8, respectively. The drug release was following super case - II transport mechanism at drug-polymer ratio 1:1 (33.33% carbomer) and it was anomalous transport at drug-polymer ratio 1:0.5 (16.66 % Carbomer). The drug release in 8 hrs was observed as 37.45, 90.62, 37.52 and 94.26% for formulation D1 to D4 respectively indicating the suitability of carbopol in sustained release matrix tablet even at 16.66 % level. The time taken for 90% drug release was predicted as 18.9, 8.3, 27.6 and 5.8 hrs respectively for formulation D1 to D4. The drug release in 8 hrs for the formulations containing nimodipine was observed as 41.41, 50.42, 73.83 and 77.12 % respectively for D5 to D8 (Table 2). Time taken for 90 % drug release was predicted to be 14.4, 13.4, 11.8 and 10.2 hrs for formulations D5 to D8 indicating that carbopols may be used for developing once a day formulation (Fig. 1, Table 2).

Influence of diluents: It was observed that the drug release was higher with spray dried lactose (organic diluent) than dicalcium phosphate (inorganic diluent), due to higher hydrophilicity of the organic diluent than the inorganic counterpart, resulting in faster movement of solvent front i.e. easier penetration of dissolution medium into the tablet matrix resulting in faster drug release (Fig. 1). The dug release rate with cinnarizine as well as nimodipine was observed to increase with increase in dicalcium phosphate/ carbopol and lactose/ carbopol ratio.

The results were found to be in accordance with the observations of Samani et al. where they reported that the release rate of diclofenac sodium increase with an increase in lactose / carbopol ratio (2003).

Table 2. Drug release parameters along with best fit model for drug release from matrix tablets prepared with Carbomer-974

Parameter	D1	D2	D3	D4	D5	D6	D7	D8
	Dcp974	Dsl974	Dcp.574	Dsl.574	Dcp974	Dsl974	Dcp.574	Dsl.574
Weight[a] (mg)	226.4±3.7	225.8±3.8	229.8±4.6	229.7±3.8	183.3±4.5	182.8±3.3	184.1±4.7	181.2±3.2
Hardness[a] (kg)	7.9±0.5	7.6±0.9	5.6±0.9	5.3±0.7	6.8±0.6	6.7±0.7	5.7±0.3	5.8±0.5
Friability[b] (%)	0.26	0.29	0.42	0.39	0.27	0.26	0.43	0.38
DR_{2h} (%)	8.77±0.32	18.90±1.52	11.93±1.13	56.04±2.54	4.04±0.33	8.87±0.48	32.57±4.26	42.18±3.52
DR_{8h} (%)	37.45±2.92	90.62±4.27	37.52±2.64	94.26±2.43	41.41±4.24	50.42±4.38	73.83±5.97	77.12±5.49
$t_{25\%}$ (hrs)	5.3	2.4	5.1	0.6	5.8	3.9	1.2	0.9
$t_{50\%}$ (hrs)	10.5	4.7	12.7	1.9	9.5	7.5	3.9	3.3
$t_{90\%}$ (hrs)	18.9	8.3	27.6	5.8	14.4	13.4	11.8	10.2
Best Fit Model	Zero order	Korsmeyer -Peppas	Korsmeyer -Peppas	Higuchi Matrix	Korsmeyer -Peppas	Zero order	Higuchi Matrix	Higuchi Matrix
r	0.9989	0.9954	0.9971	0.9605	0.9767	0.9943	0.9960	0.9951
K*	4.5183	10.1584	7.3089	22.1481	2.1704	4.4761	19.4248	23.7088
n*	1.0165	1.0284	0.7566	0.8459	1.3958	1.2122	0.6714	0.6104

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

Table 3. Parameters for sintered matrix tablets prepared with Carbomer-974 along with best fit model for drug release

Parameter	SD1	SD2	SD3	SD4	SD5	SD6
	ddc	dsl	ddc	dsl	ddc	dsl
Weight[a] (mg)	226.4±3.7	227.8±3.8	229.8±4.6	229.7±3.8	183.3±4.5	181.8±3.6
Hardness[a] (kg)	5.4±0.5	5.1±0.9	5.2±0.7	5.3±0.3	5.8±0.6	5.5±0.7
Friability[b] (%)	0.48	0.49	0.63	0.55	0.46	0.51
DR_{2h} (%)	38.92±1.22	72.50±5.37	12.99±2.52	45.16±3.24	4.24±0.36	13.18±1.02
DR_{8h} (%)	94.34±3.12	99.82±4.58	36.82±4.63	93.96±4.46	44.63±4.52	56.52±3.95
$t_{25\%}$ (hrs)	1.4	0.3	4.7	0.8	4.7	3.4
$t_{50\%}$ (hrs)	3.0	1.4	12.8	2.4	8.8	6.5
$t_{90\%}$ (hrs)	5.5	4.7	29.8	6.7	15.3	11.2
Best Fit Model	Zero Order	Higuchi Matrix	Korsmeyer-Peppas	Higuchi Matrix	Zero Order	Korsmeyer-Peppas
r	0.9952	0.9376	0.9988	0.9821	0.9727	0.9970
K*	18.1965	32.3960	8.5396	19.4582	3.7335	6.6283
n*	0.9574	0.6757	0.6940	0.8637	1.1285	1.0808

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

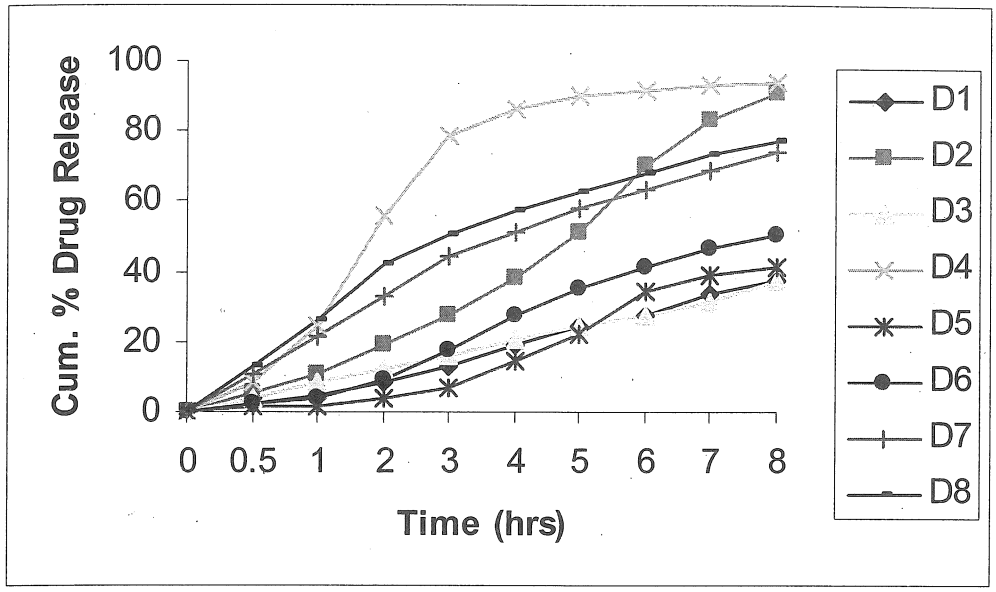

Fig 1. Drug release from carbopol-974 matrix tablets

The time taken for 25% drug release (t_{25}%) in formulations containing spray dried lactose (D2, D4, D6 and D8) was observed to be 2.4, 0.6, 3.9 and 0.9 hrs respectively in comparison to the formulations containing dicalcium phosphate D1, D3, D5 and D7 (t_{25}% = 5.3, 5.1, 5.8 and 1.2 hrs respectively) as shown in Table 2 indicating faster drug release with spray dried lactose with comparison to dicalcium phosphate in initial hours.

Effect of thermal treatment: It was observed that the drug release was slightly higher in most of the cases with thermal treatment (Fig. 2, Table 3), however, the effect was more pronounced with dicalcium phosphate (inorganic diluent). The best-fit model of drug release was zero order at higher concentration of carbopol with inorganic diluent for batch SD1 and SD5 for both drugs. At same concentration of carbopol with hydrophilic diluent the drug release was found to be dependent on nature of drug and with cinnarizine best fit model was observed as Higuchi matrix (SD2, n = 0.6757) and with nimodipine the drug release mechanism was anomalous transport for batch SD6 (n = 1.0808). In general, thermal treatment resulted in an increase in

the drug release due to change in crystallinity of both the drug and the diluent followed by decreased gelling property of carbopol.

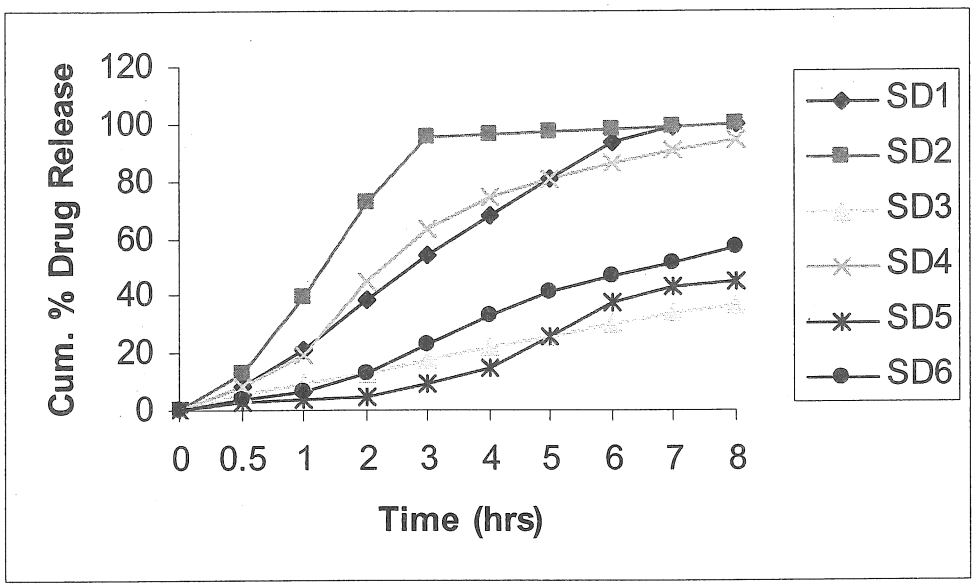

Fig 2. Drug release from Carbopol-974 matrix tablets after thermal treatment

Conclusion

This study provided an insight into the release mechanism of cinnarizine and nimodipine from carbopol matrix tablets and the significance of nature of the diluent. The release of Cinnarizine as well as nimodipine from matrix tablets at 33% carbopol level was slow and release mechanism was super case II transport whereas at lower carbopol level (16.66%) the drug release mechanism was anomalous transport. Nature of excipient was also observed to be important and more hydrophilic excipient increases the drug release though it is also dependent on the hydrophilicity of drug.

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