CONTROLLED RELEASE ORAL DELIVERY SYSTEM CONTAININGWATER INSOLUBLE DRUG

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ABSTRACT

The objective of this study was to formulate control release oral delivery system and to investigate the influence of different diluents, Carbopol 934P concentration and granulation technique in the release of poorly water-soluble drug (Ibuprofen) from Carbopol 934P matrix tablets. Matrix tablets were prepared by direct compression, wet granulation and dry granulation method at different polymer concentration using lactose, dibasic calcium phosphate (DCP), microcrystalline cellulose (MCC) and starch as diluents. Dissolution studies were carried out in 900 ml phosphate buffer pH 7.4 using USP-apparatus I. At 5% Carbopol 934P concentration, the $t_{50\%}$ was found in the rank order of tablets containing starch<MCC<DCP<lactose. The integrity of tablets and drug release were primarily governed by the properties of diluents at low polymer concentration. At 12.5% Carbopol 934P concentration, the $t_{50\%}$ was found in the rank order of tablets containing MCC<DCP<Starch<Lactose. The effect of polymer predominated as the polymer concentration increased. Similar release profiles were observed at 20% Carbopol 934P concentration with $t_{50\%}$ (>9hrs). Drug release rate decreased with polymer concentration. Granulation technique had appreciable effect on drug release profile which was in the rank order of direct compression<dry granulation<wet granulation (alcohol) <wet granulation (water). There was a significant effect of granulation technique, polymer concentration in the drug (Ibuprofen) release rate from Carbopol 934P matrix based tablets (ANOVA, $p<0.05$). Diluents have appreciable effect on drug release rate only at low polymer concentration.

INTRODUCTION

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patience compliance, least sterility constraints and flexible design of dosage forms. One of the methods of fabricating controlled release drug delivery system is by using hydrophilic matrices, also referred as hydrogels. Different polymers are employed due to their in situ gel forming characteristics, and their ability to release entrapped drug in the specific medium by swelling and cross-linking.

Carbopol, the polymers of acrylic acid, has been extensively used in the formulation of various dosage forms e.g. swellable tablets, buccal tablets, chewable tablets, effervescent tablets, suppositories, and gels forms to modify the drug release due to their gel forming characteristics (B. F. Goodrich Bulletin, 2003).

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 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, 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 (B. F. Goodrich Bulletin, 2003).

Many authors have investigated effects of excipients on the dissolution and the release from the hydrophilic polymers. Vargas and Ghaly, 1999 have evaluated the effect of excipients type on the release from HPMC matrixes. Khan and Jiabi, 1998, 1999 have observed the influence of the co-excipients on the release rate of the ibuprofen from matrix tablets containing Ibuprofen. Similarly Russlo LI and Ghaly, 2002 have also evaluated the effect of the polymer level and diluent type on the release of theophylline from Carbopol 934 matrixes.

The objective of the present study was to formulate and investigate the influence of different diluents polymer concentration and granulation technique in the release of Ibuprofen from Carbopol 934P matrices.

MATERIALAND METHOD

Ibuprofen (BN C602117) and Carbopol 934P NF (Lot No. CC05JBB570) was received as a gift sample from National Health Care Pvt. Ltd., Nepal and Noveon, Inc, Cleveland, USA respectively. Starch (BN AI5531) and Dibasic Calcium Phosphate (Lot No. B 916) was obtained as a gift from National Starch & Chemical, New Jersey, USA and Pen west, England respectively. Lactose fast flow was obtained as a gift from Pfizer, Sandwich England. Other ingredients Avicel (BN 283), magnesium stearate and talc were used in the study.

Formulation of Matrix tablets by Direct Compression:
Tablets were formulated according to Table1. Direct compression method was employed for formulations L_1 to S_3. All the components except lubricants (1% magnesium stearate and 1% talc) were added in 1 kg bottle and shaken for 15 minutes followed by addition of lubricants and further mixed for 4 min. The resulting mixture was fed into the die of 10-station tablet machine (Rimek Minipress-I, India) to produce tablets of 600 mg using flat punches of 13 mm diameter.

Formulation of Matrix tablets by Wet granulation:
Formulation M_4 (alcohol) and M_5 (water) were prepared by wet granulation method using dehydrated alcohol and water as solvent respectively. All the components except lubricants were mixed for 15 minutes in the plastic bag. 27 ml of the solvent was added and manually granulated using sieve no. 10. The granules were dried in hot air oven at 40ºC for 3 hours. The semidried granules were again passed through sieve no. 16. The granules were further dried at same temperature to obtain dried granules. Lubricants were added and mixed in plastic bag for 4 minutes. The resulting mixture was fed into the die of 10-station tablet machine (Rimek Minipress-I, India) to produce tablets of 600 mg using flat punches of 13 mm diameter.

Formulation of Matrix tablets by Dry Granulation:
Formulation M_6 (dry) prepared by dry granulation method. All the components except lubricants were mixed in the plastic bag. 2 gm slugs of 4-5 kg hardness were prepared using 10-station tablet machine (Rimek Minipress-I, India). The granules were prepared by crushing the slug in mortal and pestle and passed through the sieve no 16. Lubricants were added and further mixed for 4 min. The resulting mixture was fed into the die of 10-station

tablet machine (Rimek Minipress-I, India) to produce tablets of 600 mg using flat punches of 13 mm diameter.

Physical characterization of matrix tablets:
Uniformity of weight: 20 tablets from each batch were weighed individually using analytical balance (Ohaus-E2, USA) and standard deviations were calculated.

Thickness and diameter: The crown thickness and diameter of 10 tablets from each batch were determined using vernier caliper (Digital caliper-500-196, Japan) and standard deviations were calculated.

Hardness: 10 tablets from each batch were determined using tablet hardness tester (TBH 210, Erweka, Germany) at constant speed and standard deviations were calculated.

Assay:
10 tablets from each batch were pulverized, and three samples of 600 mg each were transferred to 500 ml volumetric flask. Initially about 300 ml of phosphate buffer (pH 7.4) was added and allowed to hydrate for 15 hour. Samples were stirred for 1hour with magnetic stirrer. The volume was made up with phosphate buffer. An aliquot was filtered; 25 ml of the filtrate was diluted to 50 ml with phosphate buffer and analyzed for Ibuprofen at 264 nm (Shimazdu, UV-1601, Japan).

In-Vitro dissolution studies:
Dissolution studies were performed in 900 ml phosphate buffer (pH 7.4) thermostatically controlled at 37±0.5º using a rotating basket dissolution apparatus (Electrolab, TDT-08L, India) at the rotation speed of 100±2 rpm. 10 ml of the sample was withdrawn at predetermined time interval followed by replacement with equal volume of the dissolution medium maintained at same condition. Samples were filtered and assayed using UV spectrophotometer (Shimazdu, UV-1601, Japan) at 264 nm.

Analysis of release rate (K):
Higuchi developed model to study the release of water-soluble drug and low soluble drugs incorporated in the solid/semisolid matrixes.

$$Q=\sqrt{(D (2C - C_s) C_s t} \text{--------- (1)}$$

Where Q is the amount of the drug released in time, t per unit area, C is the initial drug concentration, C_s is the drug solubility in the matrix media, and D is the infusibility of the drug molecules in the matrix substance (Sideman and Pappas, 2001).

The simplified form of equation (1) is

$$Q= K_H t^{1/2} \quad \text{----------(2)}$$

Where K is the Higuchi dissolution constant. Equation (2) was used to determine the release rate of different formulation. The release of the different formulation was obtained by plotting the graph between amounts of drug release versus √t.

Statistical analysis:
The release rate (K) of different formulations were compared using one-way ANOVA at $p<0.5$. The statistical analysis was performed using Statistical Package for Social Science (SPSS) version 11.

RESULTS AND DISCUSSION

Physical characterization of Tablets:
The physical characterization of the formulated tablets (weight, hardness, thickness and diameter) was performed and listed in Table 2. The variations in weight, thickness and diameter of randomly sampled tablets from each formulation were less than 2%. Sticking was observed in the formulation D1 above 150N. The assay results were found between 95%-103% for all formulation.

Dissolution studies:
Rapid gel formation was observed macroscopically in all formulations during dissolution studies (pH 7.4). Carbopol highly swells when exposed to pH environment above its pKa of 6±0.5. The rapid gel formation may be due to the ionization of carboxyl ate group, resulting in repulsion between the negative particles that adds swelling of polymer (B. F. Goodrich Bulletin, 2003). This swelling is thought to be responsible for controlling the release of drug.

The $t_{50\%}$ and Higuchi constant 'K' is listed in Table 3. High values of correlation coefficient (r^2: 0.92-0.999) were obtained when fitted to Higuchi equation as compared to first order and zero order equations.

Effect of diluents at various polymer concentration:
The comparative dissolution profile of different formulation containing 5% polymer concentration is shown in Figure 1. Significant divergence in the release profile was observed in 5% carbopol concentration using different diluents. The divergence between the dissolution profiles of different formulations may be attributed to their difference in solubility of diluents and their subsequent effect to their tortuosity factor. The $t_{50\%}$ of different formulations was found in rank order of $S_1 > M_1 > D_1 > L_1$. In S_1 disintegrating property of starch was predominant and the gel layer formed around the tablet was not supposed to be sufficiently strong to control the release of drug. Previous study suggested that starch when used with carbopol polymer; the rate of swelling of this tablet was extremely high, resulting in the exploding of gelatinous barrier and dose dumping (B. F. Goodrich Bulletin, 2003).

The low $t_{50\%}$ of M_1 may be due to its inherent disintegrating characteristics of MCC (Russo & Ghaly, 2002). Similarly $t_{50\%}$ of D_1 was found to be low. Jivrag, Martini and Thomson, 2000 suggested that when placed in water, DCP tablets are rapidly and completely penetrated by solvents. This rapid penetration is caused by the hydrophilic nature of co-excipients and the high porosity of the tablets (Jivrag, Martini & Thomson, 2000). The longer $t_{50\%}$ was observed in L_1 in comparison to other formulation. Lactose has the significant drawback of relatively slow disintegration as compared to other diluents in conventional tablets. Khan found similar result with lactose having least release when compared to tablet with starch and MCC (Khan & Jiabi, 1998, 1999).

The dissolution profile of different formulation containing 12.5 % Carbopol 934P is shown in Figure 2. It can be inferred from the dissolution profile that as the Carbopol 934P concentration is increased up to 12.5%, controlled release property is exhibited by all formulation. The disintegration characteristics of MCC and starch are masked by higher

polymer concentration. The $t_{50\%}$ was found rank in order of $M_2<D_2<S_2<L_2$. Significant differences in release rate (K) were found between formulations M_2, D_2, S_2 and L_2 (ANOVA, $p<0.05$) without any significant difference between release rates of D_2 and L_2 (ANOVA, $p>0.05$).

The dissolution profile of different formulation containing 20% polymer concentration is shown in Figure 3. All the formulations exhibited slow release of drug. The $t_{50\%}$ of all formulations was above 9 hrs. The effect of polymer predominated and the major effect of diluents was not observed at this polymer concentration. But significant differences in the release rates (K) were found between the formulations M_3, D_3, S_3 and L_3 (ANOVA, $p<0.05$), however no significant difference was found between L_3 and S_3 (ANOVA, $p>0.05$).

Effect of Polymer concentration:
Figure 4 shows the release of Ibuprofen from matrix containing dibasic calcium phosphate as diluent at different polymer concentration. The $t_{50\%}$ was found in order of $D_1> D_2 >D_3$. Similar results were found in the tablets containing starch, MCC and lactose as diluent. As the concentration of Carbopol 934P increased the rate of release become slower and linear. The reason for this could be that the gel layer formed around the tablet becomes stronger, with few interstitial spaces between the microgels (B. F. Goodrich Bulletin, 2003). Data also suggested that the standard deviation in the release profile of the formulations declines with the increase in polymer concentration. Significant difference between the release rates of different formulation with same diluent was observed using one-way ANOVA ($p<0.05$).
Effect of Granulation method:

Figure 5 shows the comparative study of the release of Ibuprofen from matrix-based tablets prepared by different granulation technique. The tablets prepared by wet granulation technique could not maintain its integrity and released more than 70% of the drugs within 1 hour. The tablets disintegrated within 1 hour thus producing more surface area for drug release. It has been explained that the tablets formulated with wet granulation method have faster release in comparison to direct compression method (BF Goodrich Bulletin, 2003). Within the wet granulation technique the tablets prepared with water as solvent released faster as compared to dehydrated alcohol. Marginal difference in release profile may be due to the fact that in case of water it made the polymer swelled beforehand. The tablets prepared by dry granulation and direct compression did not disintegrate and drug release was slow. In direct compression fine powders were used which may make very little void space for dissolution media to enter initially. Whereas in the dry granulation technique the compactness will be less thus the media might have entered faster and thus initial release was faster. Once the swelling had been achieved to same extent, the release profiles became similar.

Different diluents, polymer concentrations and granulation techniques have significant effect in the release of poorly water-soluble drug from matrix-based tablets. Diluents have appreciable effect on drug release rate only at low polymer concentration. Polymer concentrations were found to be inversely proportional to release rate in all formulations. The granulation technique also exhibited significant effect on drug release rate in the order of direct compression<dry granulation<wet granulation (using alcohol) <wet granulation (using water).

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LEGENDS

Table 1: Composition of matrix tablets.

Table 2: Physical characterization of matrix tablets.

Table 3: Release rate and $t_{50\%}$ of ibuprofen release from the matrix tablets (n=6).

Figure 1: Effect of diluent type on drug release from matrices containing 5% carbopol 934P (n=6).

Figure 2: Effect of diluent type on drug release from matrices containing 12.5% carbopol 934P (n=6).

Figure 3: Effect of diluent type on the drug release from matrices containing 20% carbopol 934P (n=6).

Figure 4: Effect of carbopol 934P concentration on the drug release from matrices containing dibasic calcium phosphate as diluent (n=6).

Figure 5: Effect of granulation technique on the drug release from matrices (n=6).

Table 1

Batch Code	Carbopol 934P (%)	Ibuprofen (%)	Diluent
L_1	5	50	43% of Lactose
L_2	12.5	50	35.5% of Lactose
L_3	20	50	28% of Lactose
M_1	5	50	43% of MCC
M_2	12.5	50	35.5% of MCC
M_3	20	50	28% of MCC
D_1	5	50	43% of DCP
D_2	12.5	50	35.5% of DCP
D_3	20	50	28% of DCP
S_1	5	50	43 of Starch
S_2	12.5	50	35.5% of Starch
S_3	20	50	28% of Starch
M_4, M_5	12.5	50	35.5% of MCC
M_6	12.5	50	35.5% of MCC

MCC= Microcrystalline Cellulose, DCP= Dibasic Calcium Phosphate

Table 2

Formulation	Weight (gm)	Diameter (mm)	Thickness (mm)	Hardness (N)
	Mean ± S. D. (n=20)	Mean±S. D. (n=10)	Mean±S. D. (n=10)	Mean±S. D. (n=10)
L_1	0.59± 0.01	12.97±0.01	3.85±0.02	172.87±9.41
L_2	0.60± 0.00	13.01±0.02	3.98±0.03	199.30±7.53
L_3	0.60± 0.01	13.01±0.01	4.05±0.06	226.70±4.04
S_1	0.60± 0.01	13.00±0.02	4.06±0.06	167.11±8.94
S_2	0.60± 0.01	13.00±0.02	4.14±0.04	206.60±2.36
S_3	0.60± 0.00	13.01±0.03	4.15±0.05	223.90±8.77
M_1	0.60± 0.00	13.00±0.01	4.17±0.02	207.90±1.06
M_2	0.60± 0.01	13.01±0.04	4.21±0.02	247.70±1.39
M_3	0.60± 0.01	13.00±0.01	4.38±0.04	252.20±3.22
D_1	0.60± 0.01	13.02±0.03	3.43±0.04	136.10±3.50
D_2	0.60± 0.01	13.02±0.03	3.54±0.05	183.44±4.20
D_3	0.60± 0.01	13.04±0.05	3.54±0.04	200.90±4.65
M_4	0.58± 0.01	13.04±0.02	3.84±0.07	224.83±4.22
M_5	0.58± 0.01	13.05±0.05	3.83±0.09	222.57±7.74
M_6	0.59± 0.01	13.03±0.02	3.89±0.06	213.00±1.01

Table 3

Formulation	K (hour $^{-0.5}$)	$t_{50\%}$ (hour)
	Mean ± SD (n=6)	Mean ± SD (n=6)
L_1	-	<1
L_2	0.222 ± 0.013	5.083 ± 0.585
L_3	0.129 ± 0.011	>9
S_1	0.518 ± 0.066	1.792 ± 0.188
S_2	0.212 ± 0.01	4.667 ± 0.204
S_3	0.147 ± 0.01	>9
M_1	0.233 ± 0.021	5.958 ± 0.781
M_2	0.175 ± 0.023	8.625 ± 1.212
M_3	0.122 ± 0.012	>9
D_1	0.648 ± 0.053	1.72 ± 0.433
D_2	0.265 ± 0.014	3.25 ± 0.418
D_3	0.188 ± 0.027	>9
M_4	-	<1
M_5	-	<1
M_6	-	<1

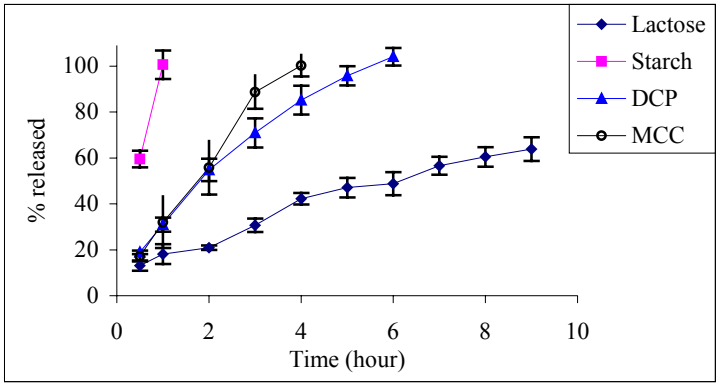


Figure 1

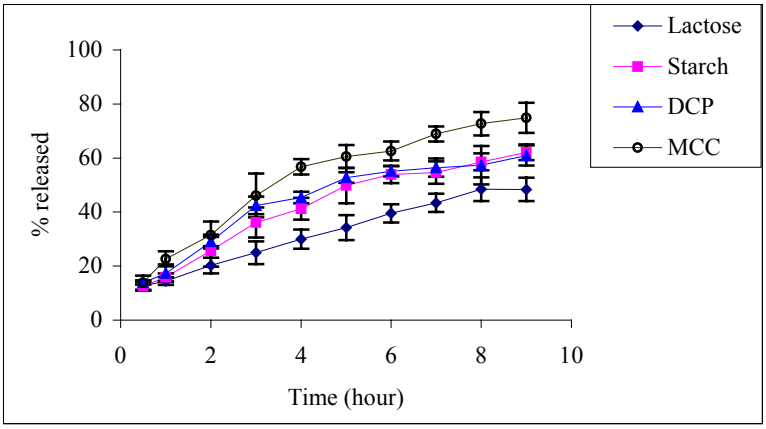
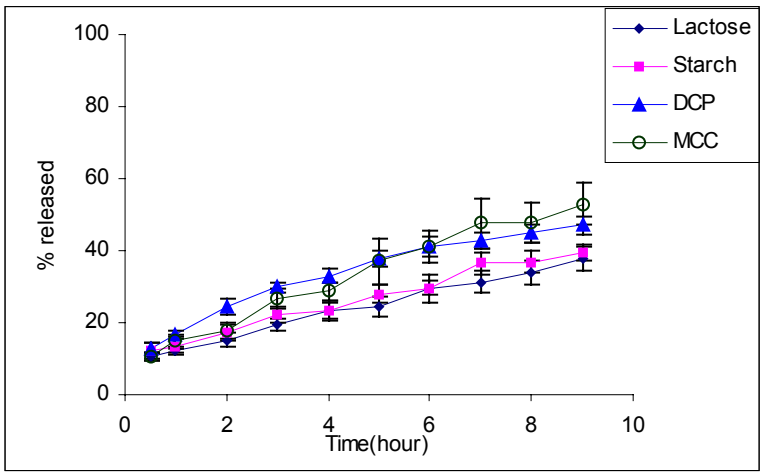


Figure 2



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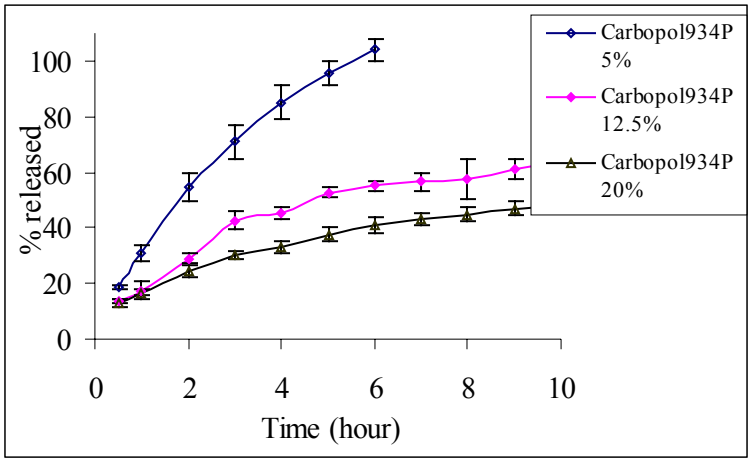

Figure 4

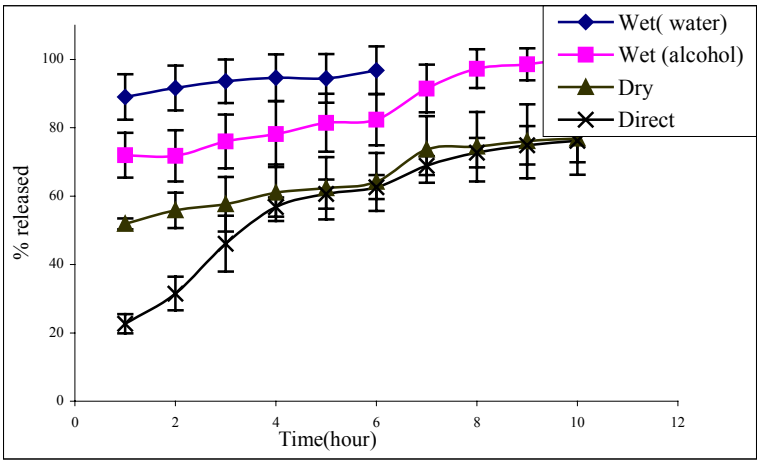

Figure 5