Chapter 5

MODIFIED GUAR GUM AS HYDROPHILIC MATRICES FOR ORAL CONTROLLED RELEASE DRUG DELIVERY

5.1 INTRODUCTION

Recent years have witnessed a greater focus on the development of sustained/controlled release drug delivery systems. See-saw fluctuations of drug concentrations are observed in systemic circulation and tissue compartments on administration of drugs in conventional dosage forms. Drug concentrations can be maintained within a narrow therapeutic range by the use of controlled - release drug delivery systems, which also minimize the incidence and severity of adverse side effects(1). In order to develop sustained or controlled release oral delivery systems the formulation scientists face the difficulties of restraining and localising the system at targeted areas of the gastro-intestinal tract (GIT). Water-soluble drugs are considered difficult to deliver in the form of sustained or controlled release preparation due to their susceptibility to dose-dumping phenomenon. Despite significant interest and numerous reports about the design of sustained or controlled release delivery systems for various water soluble drugs, very few have been successful. The oral sustained or controlled delivery systems usually include diffusion-controlled systems where the drug is uniformly distributed (dissolved or dispersed) throughout a solid matrix and the release of the drug is controlled or sustained either by incorporating hydrophobic filler (or fillers) within the matrix or by coating the drug matrix with swellable or non-swellable polymer film (or films). Hydrophilic polymers have been widely used nowadays in the development of oral controlled release delivery systems, which include the cellulose ethers, acrylates and also the natural gums(2).

GG, a naturally occurring galactomannan macromolecular hydrogel, with its high intrinsic viscosity, hot and cold water swellability and non toxicity seems to have a very high potential for use as hydrophilic matrix for controlled release tablets. In the present studies various tablet formulations

with GG and modified GGs as hydrophilic matrices have been fabricated. Preliminary screening of these formulations has been done by measuring gel strength of the hydrated matrix preparations. The swelling characteristics and dissolution profile of formulations with GG/modified GG matrices have been studied and compared with those of the widely used cellulose polymer matrix like HPMC. An attempt has also been made to study the mechanism of drug release through the matrices. Further more, the promising formulations have been evaluated *in vivo* in human volunteers using urinary excretion data.

5.2 MATERIALS

GG and Modified GG products (HGGs, MGGs, OGGs and NaCMGs), sodium dihyrogen phosphate A.R., disodium hydrogen phosphate A.R. (S.D. Fine Chem Pvt Ltd., Boisar), hydrochloric acid concentrated A.R. (Qualigens Chemicals, Bombay), lactose (Lactose (India) Limited, Baroda), microcrystalline cellulose, starch, talc, magnesium stearate (Chemicals Supply Corporation, Bombay), polyvinylpyrrolidone K-30 (Shreyas Chemicals, Bombay), dibasic calcium phosphate dihydrate (Best Chemicals, Ahmedabad), hydroxypropylmethylcellulose K4M (HPMC) (Dow Chemicals, Bombay).

5.3 EQUIPMENTS

Single-stroke compression machine (Cadmach Machineries, Ahmedabad), Dissolution apparatus (Veego Scientific Instruments, Bombay), UV-Visible Spectrophotometer (Hitachi U-2000, Japan), Analytical balance (National Scientific Instruments, Bombay), High Performance Liquid Chromatograph (Waters 501, Bangalore) Standard pipettes and burettes and other glass apparatus of Borosil (India) Limited, Mumbai were used.

5.4 REAGENTS

(i) Hydrochloric acid, 0.1N : 8.5ml of hydrochloric acid was diluted to 1000ml with water to get 0.1N HCl.

(ii) Phosphate buffer, pH 5.4: 6.8g of potassium dihydrogen phosphate was dissolved in 1000ml of water and pH was adjusted to 5.4 with 10M potassium hydroxide.

(iii)Phosphate buffer, pH 6.8: 28.80g of disodium hydrogen phosphate and 11.45g of potassium dihydrogen phosphate were dissolved in sufficient water to produce 1000ml.

(iv)Phosphate buffer, pH 7.4: 50.0ml of 0.2M potassium hydrogen phosphate was placed in a 200ml volumetric flask, 39.1ml of 0.2M sodium hydroxide was added and then water was added to volume.

5.5 METHODS

5.5.1 Tabletting :

Tablets were prepared both by wet granulation and direct compression technique on single stroke compression machine using flat face bevelled edge die-punch set, with following specifications-

Average weight	-	200mg ± 3 %
Diameter	-	8.0 ± 0.1 mm
Thickness	-	2.6 ± 0.2 mm
Hardness	-	3.5 ± 0.5 kg/cm^2

The composition of GG/modified GG matrix tablets is shown in Table 5.1.1, 5.1.2 and 5.1.3. PVP was used as 25% w/v solution in isopropyl alcohol for preparation of matrices by wet granulation technique.

5.5.2 Gel strength :

Preliminary screening of the hydrophilic matrices was done by measuring the gel strength. The hydrophilic matrix tablets were exposed to 50 ml of purified water in a petri dish of 4.5 ± 0.2 cm diameter for a period of 8h.

TABLE 5.1.1 Composition of formulations with CPM.

Formul. No.	Quantity (mg)/tablet							
	CPM	Hydrogel	Lactose	MCC	DCP	PVP	Magnesium Stearate	Talc
F#XC1	8	-	178	-	-	10	2	2
F#XC2	8	20	158	-	-	10	2	2
F#XC3	8	40	138	-	-	10	2	2
F#XC4	8	60	118	-	-	10	2	2
F#XC5	8	80	98	-	-	10	2	2
F#XC6	8	100	78	-	-	10	2	2
F#XC7	8	80	49	49	-	10	2	2
F#XC8	8	80	-	98	-	10	2	2
F#XC9	8	80	49	-	49	10	2	2
F#XC10	8	80	-	-	98	10	2	2

Where X is GG for guar gum; HG for hydrolysed guar gum; MG for methylated guar gum; OG for oxidised guar gum; and CG for sodium carboxymethylguar gum.

TABLE 5.1.2 Composition of formulations with DIL.

Formul. No.	Quantity (mg)/tablet							
	DIL	Hydrogel	Lactose	MCC	DCP	PVP	Magnesium Stearate	Talc
F#XD1	90	-	-	-	96	10	2	2
F#XD2	90	20	-	-	76	10	2	2
F#XD3	90	40	-	-	56	10	2	2
F#XD4	90	60	-	-	36	10	2	2
F#XD5	90	80	-	-	16	10	2	2
F#XD6	90	100	-	-	-	10	2	2
F#XD7	90	80	08	-	08	10	2	2
F#XD8	90	80	16	-	-	10	2	2
F#XD9	90	80	-	08	08	10	2	2
F#XD10	90	80	-	16	08	10	2	2

Where X is GG for guar gum; HG for hydrolysed guar gum; MG for methylated guar gum; OG for oxidised guar gum; and CG for sodium carboxymethylguar gum.

TABLE 5.1.3 Composition of formulations with PPA.

Formul. No.	* Quantity (mg)/tablet					
	PPA	Hydrogel	Lactose	PVP	Magnesium stearate	Talc
F#P1	75	GG	51	10	2	2
F#P2	75	HG23	51	10	2	2
F#P3	75	MG3	51	10	2	2
F#P4	75	HPMC	51	10	2	2

* 80 mg/Tablet hydrogels were used in each case.

purified water in a petri dish of 4.5 ± 0.2 cm diameter for a period of 8h. Gel strength of these hydrated matrices was measured as described by van Aerde *et al*(3), using the apparatus shown in Fig 5.1. A beaker was balanced on one plate of two armed balance at the underside of which a cone shaped pin was fixed. Water was continuously added to the beaker due to which the pin exerted an increasing force on the tablet. The gel strength was defined as total amount of water(ml) necessary to perforate the tablet.

Gel strength of hydrated matrices was determined in triplicate for each of 3 batches of the modified products. Mean (n = 9) alongwith the standard error are recorded in Table 5.2 A and 5.2B.

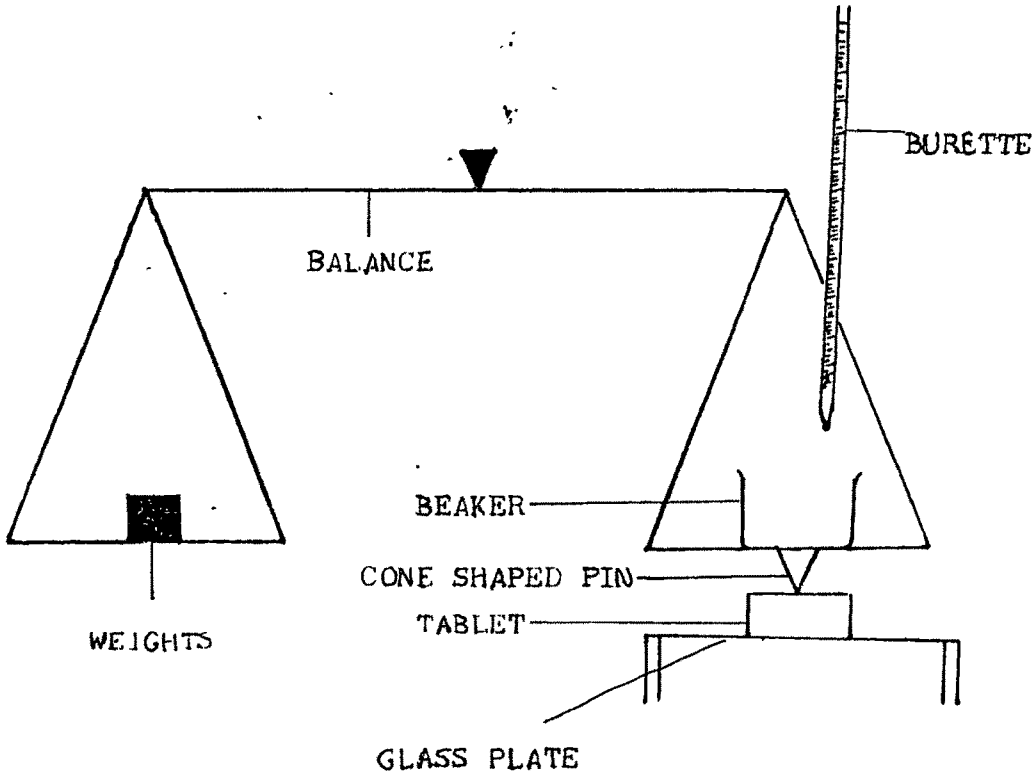
5.5.3 Swelling characteristics :

Water penetration and subsequent swelling characteristics of the matrices were studied, by recording the change in the tablet dimensions, radius and thickness, on exposure of the tablets to purified water in petri dish, with respect to time. The changes in the tablet surface area, calculated from the radius and thickness of the hydrated tablets, are recorded in Table 5.3. A comparative swelling of GG and HPMC after 30 minutes has been shown in Fig 5.2.2.

Tablets subjected to dissolution studies were removed at the sampling time points, dried completely to a moisture content value of below 1 % w/w and the weight of these dried tablets was noted, to study the erosion of the tablet surface. The decline in the weight after dissolution of GG/HGG/MGG/HPMC matrix tablets is shown in Fig 5.3.

5.5.4 Dissolution studies :

Dissolution studies were performed using USP XXII (4) apparatus 1 (basket assembly) at 100 rpm. 900 ml of purified water maintained at 37° ± 0.5°C


BURETTE
BALANCE
BEAKER
CONE SHAPED PIN
TABLET
WEIGHTS
GLASS PLATE

was used as dissolution medium. 5ml samples were withdrawn at regular intervals and replaced with fresh dissolution media. Samples were filtered and assayed spectrophotometrically on Hitachi U-2000 spectrophotometer.

All dissolution studies were carried out in triplicate for three different batches of each formulation on three consecutive days. The average of these values alongwith the standard error are recorded in Table 5.4.1 to 5.4.6. A comparison of cumulative percent drug released at time 0.5h, 1.0h, 2.0h and 8.0h from the matrices is shown graphically in Fig 5.4.1 to 5.4.6.

5.5.5 In vivo Evaluation :

A single dose complete cross over study for each of the promising formulations was performed for *in vivo* evaluation. 12 healthy male human volunteers of age between 22 and 26 years and weighing between 55 and 70 kgs were selected for the study. The volunteers were divided into four groups containing three volunteers each. The volunteers of each group were administered one matrix (GG, HPMC, HGG, MGG) tablet, each containing 75 mg of PPA, with 200ml water following overnight fasting. It was ensured that the volunteers were not under any other treatment. Urine samples were collected at 0, 1, 2, 4, 6, 8, 12, 20, and 24 hours. Volume of urine was measured and representative samples were refrigerated till analysed.

Wash out period of one week was allowed in case of each volunteer till each of them received all types of the formulations. Samples were extracted and analysed by HPLC as reported by R.Dowse *et al* (5). The results are recorded in Table 5.5.3 and represented graphically in Fig 5.5.2.

5.6 DATA ANALYSIS

Gel strength of the matrices was measured in terms of amount(ml) of water needed to perforate the hydrated matrix tablet. The values were determined in triplicate for three batches of each product and mean values (n = 9) alongwith the standard error are recorded in Table 5.2.

The surface area (S.A.) of the tablets was calculated using the following equation -

$$A = 2 \pi r h$$

where A is surface area of the tablet (sq. mm), r is the radius of the tablet (mm), and h is the thickness of tablets (mm). Mean value of six tablets of each batch was taken and 3 similar batches were evaluated on three different days for determination of rate of increase in S.A., to study the swelling characteristics of the matrix.

Mean cumulative percent drug release alongwith its standard error value was calculated at each sampling time point from 3 batches evaluated on 3 consecutive days (no. of samples = 54).

The dissolution data were fitted to the following exponential release model equation (6) to study the release kinetics of the drug from the matrix tablets -

$$M_t/M_\infty = k \times t^n$$

Where M_t/M_∞ is the fractional drug release into the dissolution medium, k is the constant which incorporates the properties of macromolecular polymeric matrix and the drug, n is the diffusional exponent which characterizes the drug transport kinetics. The values of n and k were calculated for the drug released in eight hours and are recorded in Table 5.4.1 to 5.4.6.

In vivo evaluations were performed on 12 volunteers divided into four groups containing 3 volunteers each. Each group was administered all the four types of formulations allowing one week washout period between each study. Each sample was taken in duplicate for analysis and mean cumulative amount of unchanged drug excreted in urine was determined and the results are shown in Fig 5.5.2.

All comparisons of data were done by ANOVA.

5.7 RESULTS AND DISCUSSION

GG, modified by partial acid hydrolysis, methylation, oxidation and carboxymethylation was evaluated for its potential as hydrophilic matrix formers. GG and modified GG matrix tablet formulations were developed using CPM, DIL and PPA as model drugs as per the compositions recorded in Table 5.1.1 to 5.1.3. These formulations were studied for gel strength, swelling characteristics and drug release profile *in vitro* and *in vivo*.

5.7.1 Gel Strength :

Preliminary screening of the developed tablet formulations was done by measuring the gel strength of tablets as described by van Aerde (3). These tablet preparations were exposed to water in petri dish for a period of 8h and the gel strength of the hydrated tablets was measured using the apparatus shown in Fig 5.1. The results are recorded in Table 5.2A and 5.2B. When the tablet comes in contact with water, water enters into the pores of the tablet and hydrates the gum. On hydration the polymer chains of the gum undergo transition from glassy to dynamic rubbery state which is manifested in the formation of gel. The strength of this gel layer largely depends on the polymer chain length (molecular weight) and the rate of hydration of the gum besides other factors.

Results show that there is a significant reduction in the gel strength of GG on modification either by hydrolysis, methylation, oxidation or carboxy-methylation. The modified products may be arranged in the increasing order of gel strength as

OGGs < NaCMGs < MGGs < HGGs

The tablets with OGGs disintegrate within 10 - 15 min of exposure to water. Oxidation of GG produces water-insoluble products and so there is no gel formation. Hence OGGs cannot be used as hydrophilic matrix for controlled release tablets. Tablets made using NaCMGs either disintegrate within 2h (NaCMG4, NaCMG5, NaCMG6), or become soft masses (NaCMG1, NaCMG2, NaCMG3) on hydration for 8h. The carboxyalkylation of GG involve the use of derivatizing agents like monochloroacetic acid in conjunction with strong alkali. This may involve liability of GG to the reaction conditions which causes some chain cleavage (viscosity values in Table 4.5). This results in reduced polymer molecular weight and hence the low gel strength.

Partial acid hydrolysis of GG to very low degrees result in products which form thick and cohesive gel of high strength. These products were found very promising for their use as hydrophilic matrix for controlled release tablets. Hydrolysing GG using acid of higher strength (0.3N, 0.5N) or for longer durations (4h, 5h) gives products with lower gel strength indicating the hydrolysis of mannose backbone alongwith that of galactose side chain. Hence controlled hydrolysis was done using a mixture of HCl with a polar O-containing organic solvent, methanol which prevents complete hydration of gum and provides resistance to hydrolysis (7).

GG methylated to lower degrees (MG1, MG2, MG3) reveal sufficient gel strength (Table 5.2) and can be used as matrix formers for controlled release tablets. Methylation of GG under mild conditions like low temperatures

Table 5.2A Gel Strength of Hydrated GG/HGG/MGG matrix tablets with CPM.

Formul. No.	Gel Strength (ml)	Formul. No.	Gel Strength (ml)	Formul. No.	Gel Strength (ml)	Formul. No.	Gel Strength (ml)	Formul. No.	Gel Strength (ml)
F#GGC2	17.40(0.65)	F#GGC3	22.22(0.35)	F#GGC4	31.73(0.75)	F#GGC5	38.25(0.52)	F#GGC6	51.62(0.77)
F#HG11C2	13.25(0.25)	F#HG11C3	20.22(0.57)	F#HG11C4	30.37(0.63)	F#HG11C5	33.41(0.63)	F#HG11C6	45.22(0.77)
F#HG12C2	12.27(0.38)	F#HG12C3	17.77(0.68)	F#HG12C4	29.42(0.63)	F#HG12C5	31.37(0.32)	F#HG12C6	40.27(0.45)
F#HG13C2	10.31(0.77)	F#HG13C3	17.43(0.64)	F#HG13C4	23.32(0.79)	F#HG13C5	27.40(0.57)	F#HG13C6	36.32(0.66)
F#HG14C2	08.31(0.69)	F#HG14C3	15.43(0.52)	F#HG14C4	20.27(0.38)	F#HG14C5	22.30(0.68)	F#HG14C6	32.71(0.59)
F#HG15C2	-	F#HG15C3	09.91(0.57)	F#HG15C4	18.85(0.79)	F#HG15C5	20.26(0.61)	F#HG15C6	23.71(0.63)
F#HG21C2	10.48(0.93)	F#HG21C3	15.73(0.68)	F#HG21C4	25.38(0.37)	F#HG21C5	29.77(0.89)	F#HG21C6	39.41(0.73)
F#HG22C2	08.12(0.27)	F#HG22C3	14.37(0.49)	F#HG22C4	23.69(0.42)	F#HG22C5	25.65(0.88)	F#HG22C6	37.71(0.31)
F#HG23C2	-	F#HG23C3	07.72(0.99)	F#HG23C4	15.62(0.73)	F#HG23C5	21.05(0.56)	F#HG23C6	25.55(0.55)
F#HG24C2	-	F#HG24C3	-	F#HG24C4	06.71(0.86)	F#HG24C5	12.95(0.56)	F#HG24C6	15.72(0.89)
F#HG25C2	-	F#HG25C3	-	F#HG25C4	-	F#HG25C5	09.71(0.68)	F#HG25C6	13.31(0.56)
F#HG31C2	-	F#HG31C3	-	F#HG31C4	09.72(0.63)	F#HG31C5	12.23(0.77)	F#HG31C6	16.68(0.49)
F#HG32C2	-	F#HG32C3	-	F#HG32C4	-	F#HG32C5	06.73(0.37)	F#HG32C6	10.22(0.71)
F#HG51C2	-	F#HG51C3	-	F#HG51C4	-	F#HG51C5	-	F#HG51C6	-
F#HG52C2	-	F#HG52C3	-	F#HG52C4	-	F#HG52C5	-	F#HG52C6	-
F#MG1C2	-	F#MG1C3	10.25(0.30)	F#MG1C4	20.22(0.62)	F#MG1C5	24.50(0.80)	F#MG1C6	27.60(1.00)
F#MG2C2	-	F#MG2C3	09.45(0.50)	F#MG2C4	19.70(0.80)	F#MG2C5	20.30(0.65)	F#MG2C6	22.45(0.30)
F#MG3C2	-	F#MG3C3	-	F#MG3C4	15.25(0.75)	F#MG3C5	-	F#MG3C6	20.28(0.55)
F#MG4C2	-	F#MG4C3	-	F#MG4C4	-	F#MG4C5	-	F#MG4C6	-
F#MG5C2	-	F#MG5C3	-	F#MG5C4	-	F#MG5C5	-	F#MG5C6	-
F#MG6C2	-	F#MG6C3	-	F#MG6C4	-	F#MG6C5	-	F#MG6C6	-

" - " Shows that these formulations formed soft masses on hydration for 8h and did not retain dimensions.

The tablet formulations made with OGGs and NaCMGs as matrices disintegrated within one hour.

Table 5.2B Gel Strength of Hydrated GG/HGG/MGG matrix tablets with DIL.

Formul. No.	Gel Strength (ml)	Formul. No.	Gel Strength (ml)	Formul. No.	Gel Strength (ml)	Formul. No.	Gel Strength (ml)	Formul. No.	Gel Strength (ml)
F#GGD2	19.40(0.54)	F#GGD3	23.82(0.65)	F#GGD4	33.08(0.68)	F#GGD5	39.98(0.55)	F#GGD6	54.02(0.68)
F#HG11D2	13.85(0.65)	F#HG11D3	22.05(0.57)	F#HG11D4	31.67(0.45)	F#HG11D5	36.15(0.99)	F#HG11D6	46.75(0.50)
F#HG12D2	12.55(0.45)	F#HG12D3	19.08(0.73)	F#HG12D4	29.85(0.75)	F#HG12D5	34.27(0.54)	F#HG12D6	42.57(0.40)
F#HG13D2	10.97(0.65)	F#HG13D3	17.95(0.55)	F#HG13D4	25.75(0.36)	F#HG13D5	33.02(0.75)	F#HG13D6	38.25(0.65)
F#HG14D2	09.69(0.32)	F#HG14D3	16.73(0.42)	F#HG14D4	22.88(0.78)	F#HG14D5	29.40(0.68)	F#HG14D6	33.98(0.75)
F#HG15D2	-	F#HG15D3	10.08(0.46)	F#HG15D4	20.25(0.39)	F#HG15D5	21.98(0.54)	F#HG15D6	26.15(0.60)
F#HG21D2	12.08(0.56)	F#HG21D3	18.15(0.55)	F#HG21D4	28.08(0.65)	F#HG21D5	35.42(0.56)	F#HG21D6	42.10(0.53)
F#HG22D2	09.72(0.57)	F#HG22D3	15.75(0.25)	F#HG22D4	24.79(0.62)	F#HG22D5	30.75(0.68)	F#HG22D6	39.35(0.67)
F#HG23D2	-	F#HG23D3	08.75(0.99)	F#HG23D4	18.72(0.55)	F#HG23D5	25.25(0.49)	F#HG23D6	28.65(0.75)
F#HG24D2	-	F#HG24D3	-	F#HG24D4	08.96(0.66)	F#HG24D5	19.95(0.56)	F#HG24D6	18.35(0.65)
F#HG25D2	-	F#HG25D3	-	F#HG25D4	-	F#HG25D5	11.65(0.76)	F#HG25D6	14.85(0.45)
F#HG31D2	-	F#HG31D3	-	F#HG31D4	10.02(0.55)	F#HG31D5	14.79(0.37)	F#HG31D6	17.71(0.30)
F#HG32D2	-	F#HG32D3	-	F#HG32D4	-	F#HG32D5	08.25(0.47)	F#HG32D6	13.10(0.45)
F#HG51D2	-	F#HG51D3	-	F#HG51D4	-	F#HG51D5	-	F#HG51D6	-
F#HG52D2	-	F#HG52D3	-	F#HG52D4	-	F#HG52D5	-	F#HG52D6	-
F#MG1D2	-	F#MG1D3	13.15(0.50)	F#MG1D4	23.62(0.62)	F#MG1D5	25.78(0.60)	F#MG1D6	27.75(0.58)
F#MG2D2	-	F#MG2D3	11.65(0.63)	F#MG2D4	21.09(0.70)	F#MG2D5	22.41(0.75)	F#MG2D6	22.95(0.30
F#MG3D2	-	F#MG3D3	-	F#MG3D4	16.85(0.55)	F#MG3D5	19.95(0.45)	F#MG3D6	21.45(0.35)
F#MG4D2	-	F#MG4D3	-	F#MG4D4	-	F#MG4D5	09.75(0.86)	F#MG4D6	12.22(0.85)
F#MG5D2	-	F#MG5D3	-	F#MG5D4	-	F#MG5D5	-	F#MG5D6	-
F#MG6D2	-	F#MG6D3	-	F#MG6D4	-	F#MG6D5	-	F#MG6D6	-

" - " Shows that these formulations formed soft masses on hydration for 8h and did not retain dimensions.

The tablet formulations made with OGGs and NaCMGs as matrices disintegrated within one hour.

(about 4°C) and presence of a polar organic solvent, methanol, may not result in chain cleavage of the molecule as can also be observed in the viscosity values (Table 4.3). Methylation of GG further (MG4, MG5, MG6) may involve the liability of GG polymer chain causing chain cleavage and hence reduction in molecular weight and finally lower gel strength.

Thus it can be seen that GG, modified by partial acid hydrolysis and methylation to lower degrees, can be used as hydrophilic matrix for controlled release tablets.

5.7.2 Swelling Characteristics :

GG and modified GG (HGGs and MGGs) matrix tablets were exposed to water in a petri dish and evolution of tablet surface area was determined by recording the change in the radius and thickness of tablets on hydration with respect to time, to evaluate water penetration and subsequent swelling characteristics. The results are recorded in Table 5.3. The swelling behavior of GG matrix tablets can be schematically explained as in Fig 5.2.1. When the tablet surface comes in contact with water, water enters into the pores of the tablet. This causes swelling of tablet (Step1) and tablets are observed to be covered with half gelled non-cohesive mass. A major change in surface area due to swelling is noticed in first hour in case of GG tablets (0.5h - 3.425 times, 1h - 4.408 times). The hydration of gum proceeds further (from step2 to step4) resulting in formation of cohesive gel layer, which is a prerequisite for retarding drug release from gel matrix. Gel formation is a manifestation of transition of polymer chain, on hydration, from glassy state to dynamic rubbery state. The poor interaction coefficient of GG and hence poor rate of hydration makes the formation of this gel layer a very slow process. In contrast to GG matrix tablets, HPMC matrix tablets gel on surface instantaneously on exposure to water. The increase in surface area after 1 hour of exposure to water was observed to be only 2.8

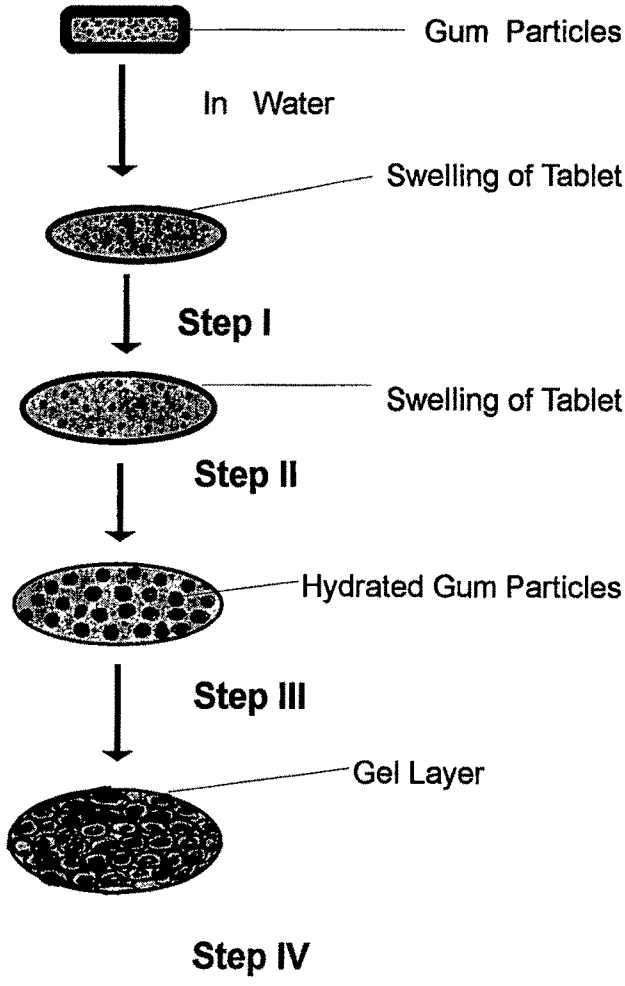
times. A comparison of the swelling characteristics of GG and HPMC matrix tablets is shown in Fig 5.2.2.

Modification of GG was undertaken to improve its rate of hydration and thereby expedite the gelling of its matrix. The formulations with modified GGs were screened by measuring the gel strength and only those formulations which had satisfactory gel strength were studied for the swelling characteristics. The results are recorded in Table 5.3.1. HGG tablet formulations show significant change in their swelling characteristics in the first hour of hydration in water compared to GG. Guar galactomannan with reduced galactose-mannose ratio has better interaction properties (8). Partial acid hydrolysis to very low degree may result in hydrolysis of galactose moiety and hence lead to a product with an improved rate of hydration. In case of formulation F#HG23C5 the increase in surface area is only 3.68 times, which suggests a significant change in the swelling characteristics of GG on hydrolysis. There is reduction of about 15% in the times increase in surface area in initial first hour of exposure to water of HGG matrices compared to GG.

Similar changes in the swelling characteristics of MGG matrix tablets was observed. The increase in surface area in 1st hour was 2.9 to 3.5 times compared to GG. This signifies that methylation of GG results in increased rate of hydration.

Tablets of formulations F#GGC5, F#HG23C5, F#MG3C5 and F#HPMC5 were subjected to dissolution studies and the weight of dried matrix tablets after dissolution was determined at each sampling time point. The results are shown in Fig 5.3. A sharp decline in the weight of dried GG matrix tablet in initial one hour (85 mg) was observed compared to HGG matrix tablets (50 mg), MGG matrix tablets (45 mg) and HPMC matrix tablets (45

Fig 5.2 Swelling Characteristics of Matrix Tablets.



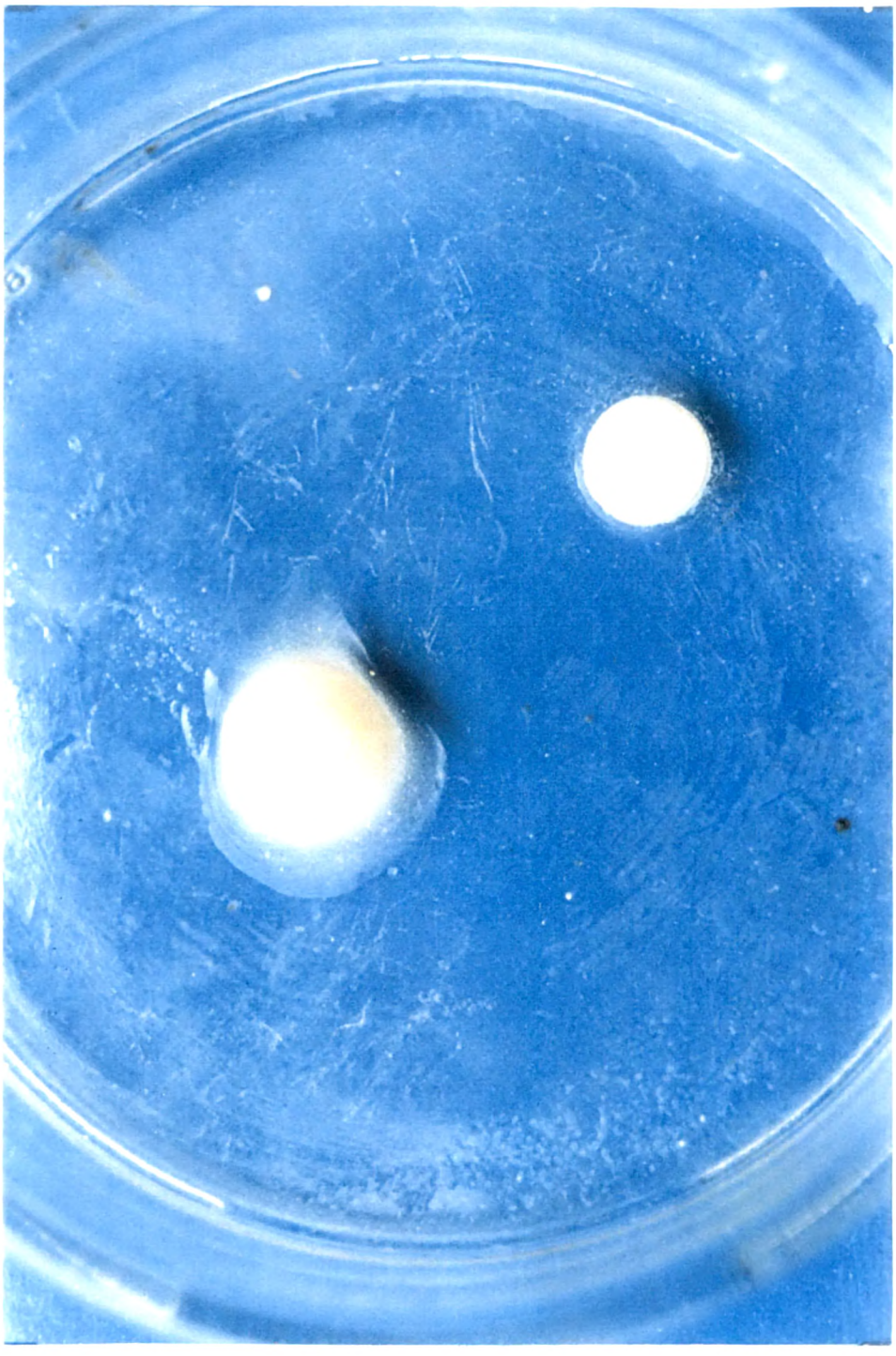


TABLE 5.3.1 Swelling characteristics of GG/HGG/MGG/HPMC matrices.

Sr. No.	Formul. No.	Surface area (sq.mm) after hydration time (h) X 3.14					
		0.00	0.50	1.00	2.00	4.00	24.00
1.	F#GGC5	20.26(0.06)	68.50(2.87)	88.15(2.87)	107.50(2.58)	117.50(1.19)	122.20(2.78)
2.	F#HG11C5	20.43(0.22)	68.72(1.79)	89.32(2.06)	109.22(2.61)	119.63(1.79)	125.21(1.63)
3.	F#HG12C5	20.26(0.07)	67.82(1.26)	88.11(2.33)	102.12(2.49)	114.41(1.57)	123.32(2.39)
4.	F#HG13C5	20.22(0.06)	65.92(1.17)	78.10(0.92)	102.48(0.97)	126.80(1.54)	131.30(2.10)
5.	F#HG14C5	19.98(0.52)	64.89(0.55)	77.00(1.27)	99.60(0.97)	116.85(1.54)	131.30(2.10)
6.	F#HG15C5	20.26(0.08)	65.42(0.67)	82.80(1.64)	102.48(2.67)	117.80(2.44)	133.62(3.37)
7.	F#HG21C5	20.09(0.37)	65.52(0.43)	77.00(0.78)	102.48(0.99)	117.80(1.47)	131.42(2.78)
8.	F#HG22C5	20.20(0.43)	64.48(0.67)	77.00(0.99)	100.43(1.04)	117.50(2.08)	133.62(1.99)
9.	F#HG23C5	20.11(0.18)	63.24(1.45)	74.12(0.74)	93.60(0.99)	112.24(1.77)	129.00(1.78)
10.	F#MG1C5	20.18(0.10)	51.23(1.23)	71.37(1.21)	90.29(2.63)	100.31(1.21)	102.31(2.31)
11.	F#MG2C5	20.26(0.62)	45.32(2.03)	65.71(2.22)	81.37(1.61)	91.37(1.77)	97.34(1.03)
12.	F#MG3C5	20.05(0.33)	38.17(2.13)	59.71(1.17)	71.28(1.91)	85.34(2.03)	90.99(1.79)
13.	F#HPMC5	20.22(0.42)	36.41(0.55)	56.65(0.88)	65.89(1.02)	78.90(1.07)	89.93(1.89)

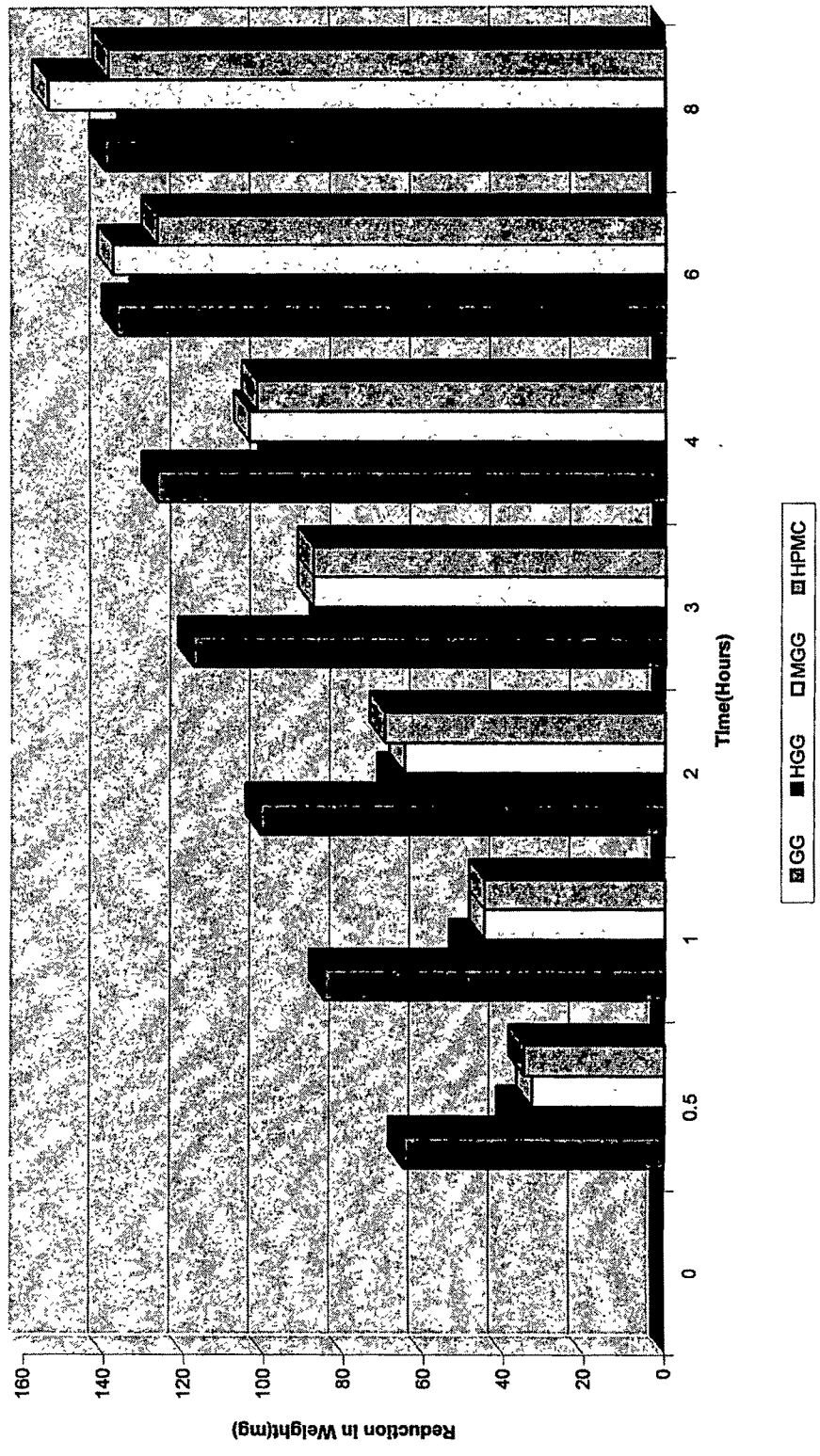


Fig 5.3 Reduction in weight of tablets after dissolution for time(h).

mg). The half gelled non-cohesive mass covering the tablet surface on exposure to water due to poor rate of hydration gets eroded easily and hence the reduction in weight. The result also confirms the improvement in rate of hydration of GG on controlled hydrolysis and methylation, whereby the gelation of tablet surface is faster.

5.7.3 Dissolution Studies :

Dissolution studies were performed using USP XXII apparatus 1 (Basket assembly) at 100 rpm. 900ml purified water maintained at 37° ± 0.5°C was used as dissolution medium in each case. The formulations with modified GG products which showed significant changes in the swelling characteristics compared to GG were evaluated *in vitro* for drug dissolution profile, using CPM and DIL as model drugs. The results of drug release profile from various formulations are recorded in Table 5.4.1 to 5.4.6 and shown graphically in Fig 5.4.1 to 5.4.6.

5.7.3.1 Effect of concentration of GG on drug release :

GG matrix formulations containing GG in concentrations ranging from 0% w/w to 50% w/w and prepared by direct compression were subjected to dissolution studies and the results are recorded in Table 5.4.1. The formulations containing 0% w/w and 10% w/w of GG were observed to disintegrate in 30 minutes and 2 hours respectively and thereby release the drug completely by this time. The release rate as a function of gum concentration shows that an inverse relationship exists between the amount of gum in the formulation and release rate of drug. The rate of drug release reduces with increase in GG concentration in the matrix tablets. The total amount of drug release in 8h from formulations with increasing concentrations of GG (100% → 20% GG ; 92.92% → 30 % GG ; 89.93% → 40% GG and 70.23% → 50% GG) show that as GG concentration increases to 50 % there is an incomplete release of drug from the matrix. The

Table 5.4.1 Effect of concentration of GG on Release of CPM.

Time(Hours)	Cumulative % drug Release(S.E.)					
	F#GGC1	F#GGC2	F#GGC3	F#GGC4	F#GGC5	F#GGC6
0.0	0.00	0.00	0.00	0.00	0.00	0.00
0.5	77.64(3.44)	50.48(3.63)	47.73(3.01)	41.06(2.22)	37.06(2.13)	30.96(2.43)
1.0	-	74.65(3.01)	60.71(2.91)	51.34(1.17)	48.32(2.93)	41.34(2.77)
2.0	-	97.61(3.11)	74.63(1.73)	68.29(2.01)	63.29(1.68)	51.49(1.73)
3.0	-	-	85.77(2.41)	80.56(1.59)	75.56(1.02)	60.69(1.60)
4.0	-	-	90.37(2.43)	86.91(0.97)	82.91(1.63)	65.91(1.69)
6.0	-	-	94.99(1.41)	90.12(1.11)	86.41(1.17)	68.71(1.69)
8.0	-	-	99.71(2.42)	92.92(0.63)	89.93(0.79)	70.23(0.71)
`K' value(%)	-	-	54.79	43.97	39.28	37.51
`n'			0.742167	0.736534	0.731428	0.692288

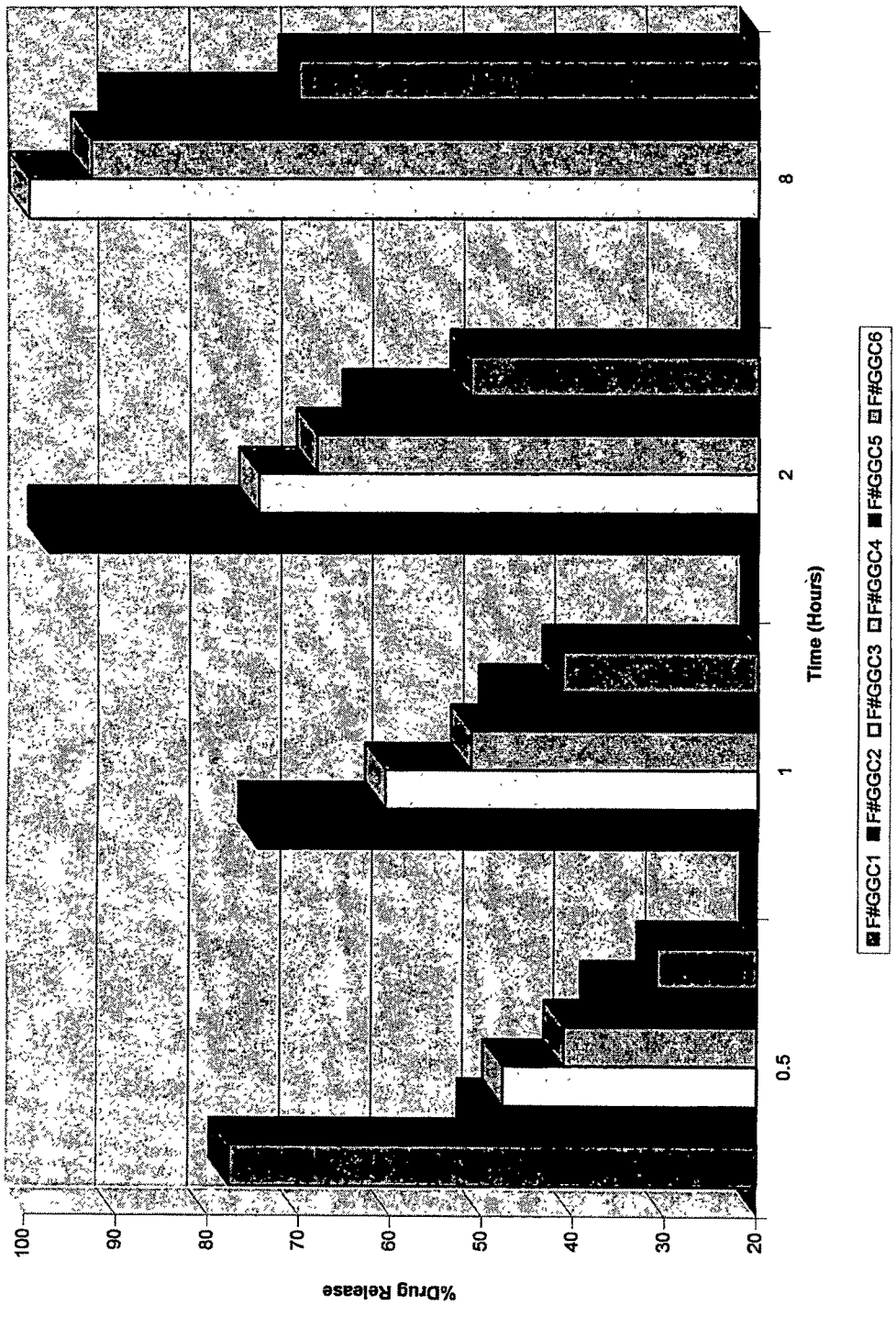


Fig 5.4.1 Effect of concentration of GG on release of CPM.

phenomena of the effect of gum concentration on drug release can be explained by the percolation theory (9). The drug clusters do not span the whole tablet and remain as isolated networks. The part of drug remains encapsulated by the polymer matrix making its release incomplete. At the GG concentrations above 20% w/w to about 40% w/w the two components, gum and drug/excipients, are uniformly distributed throughout the tablet matrix hence the drug release is controlled and complete.

The release kinetics were studied by substituting the data in the Ritgers and Peppas equation(6) and calculating the parameters `n' and `k'. The values of `n' suggest a non-Fickian type anomalous diffusion mechanism of drug release from the matrices.

5.7.3.2 Effect of Modification of GG on drug release :

GG modified by oxidation and carboxymethylation was not found suitable for use as hydrophilic matrix for controlled release tablets (gel strength). GG modified by partial acid hydrolysis and partial methylation to certain degrees, as discussed earlier, was found to be suitable for use as matrix former.

Results show that in case of GG matrix tablets there is a release of 37.06% ± 2.13 of drug in first half hour and 48.32% ± 2.93 in one hour. Thereafter the drug release decreases. The reason for this burst effect may be erosion of matrix surface as explained in terms of reduction in weight after dissolution for fixed durations and swelling characteristics. The presence of water in the pores of the tablet not only hydrates the gum but also dissolves the drug *in situ*, which gets released from the matrix. The installation of gel layer, a prerequisite for retarding drug release, takes place slowly. The gel layer once formed acts as barrier to water penetration into the tablet

Table 5.4.2 A Effect of Hydrolysis of GG on Release of CPM from HGG matrices.

Time (Hours)	Cumulative % drug Release(S.E.)							
	F#GGC5	F#HG13C5	F#HG14C5	F#HG15C5	F#HG21C5	F#HG22C5	F#HG23C5	F#HPMC5
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	37.06(2.13)	29.29(0.54)	29.93(0.54)	30.26(0.66)	27.34(1.75)	26.76(0.69)	25.65(0.23)	29.31(0.99)
1.0	48.32(2.93)	44.51(0.97)	43.43(0.97)	45.21(1.01)	42.80(1.29)	40.46(0.51)	39.31(0.96)	40.58(0.07)
2.0	63.29(1.68)	60.28(1.41)	58.90(1.39)	64.88(1.26)	54.91(1.38)	58.04(0.44)	53.73(0.54)	51.25(0.17)
3.0	75.56(1.32)	77.74(0.85)	79.00(1.72)	81.31(2.33)	73.13(1.16)	69.70(0.95)	65.55(0.34)	62.99(0.53)
4.0	82.91(1.63)	84.13(0.38)	85.41(0.69)	89.92(1.71)	77.74(0.61)	81.37(0.98)	75.68(0.34)	72.85(0.60)
6.0	85.41(1.19)	89.58(0.69)	90.23(0.73)	96.77(1.33)	84.13(0.40)	88.06(0.69)	83.72(0.47)	82.70(0.42)
8.0	89.94(0.79)	93.63(0.42)	93.20(0.71)	98.32(1.79)	92.81(0.42)	94.32(0.64)	90.31(0.26)	94.36(0.76)
`K' value (%)	39.28	28.22	28.18	27.87	26.50	24.68	24.29	27.33
`n'	0.73142	0.74584	0.74616	0.75696	0.738368	0.74444	0.73484	0.72861

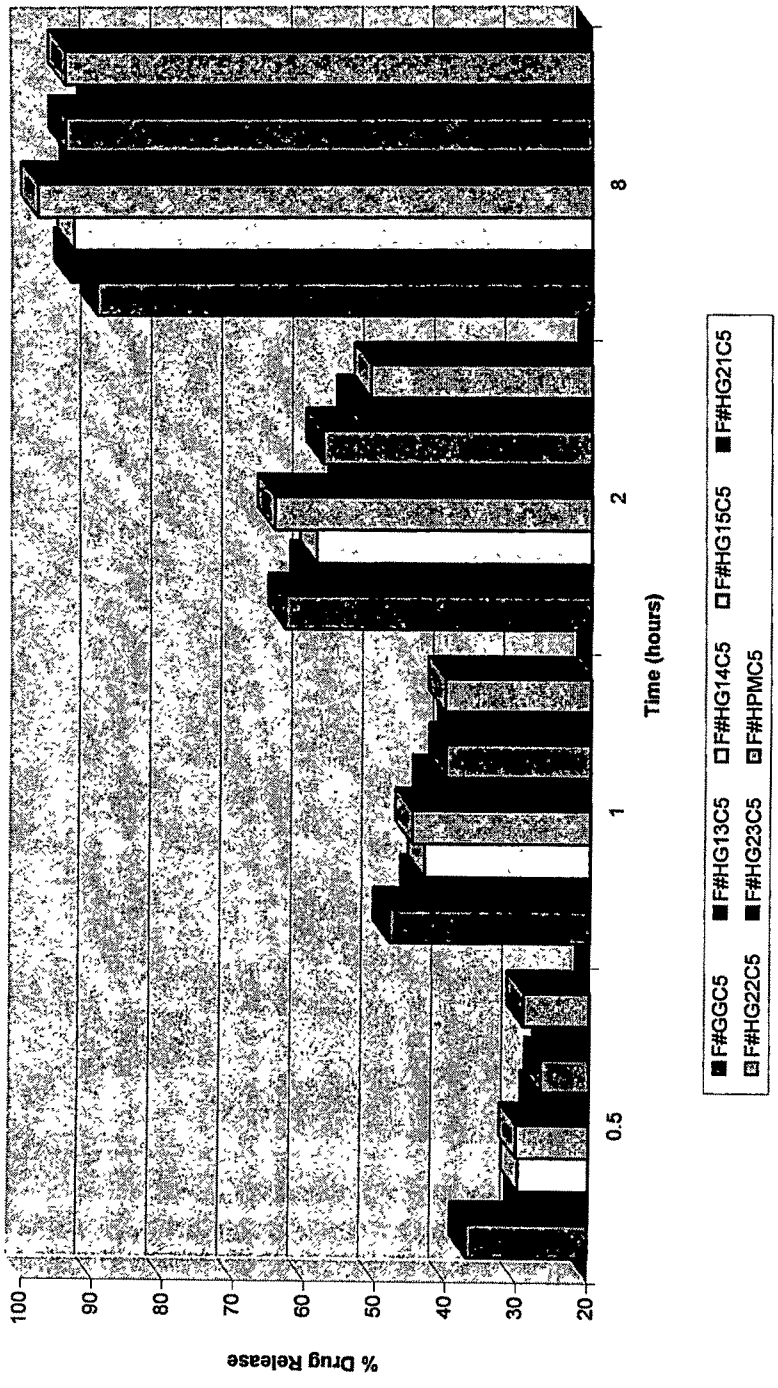


Fig 5.4.2 A Effect of hydrolysis of GG on release of CPM.

Table 5.4.2 B Effect of Hydrolysis of GG on Release of DIL from HGG matrices.

Time (Hours)	Cumulative % drug Release(S.E.)							
	F#GGD5	F#HG13D5	F#HG14D5	F#HG15D5	F#HG21D5	F#HG22D5	F#HG23D5	F#HPMD5
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	34.32 (2.44)	29.71(2.32)	29.29(2.07)	29.98(2.19)	27.43(2.71)	25.43(2.21)	25.25(2.21)	27.71(0.63)
1.0	44.45(2.03)	40.32(2.02)	41.44(2.11)	42.81(2.93)	40.46(0.72)	38.42(1.48)	37.71(1.38)	37.63(1.09)
2.0	61.32(1.72)	59.37(1.95)	58.90(1.43)	60.28(1.26)	58.04(2.11)	55.32(1.47)	53.76(1.09)	48.41(1.63)
3.0	74.23(1.09)	74.71(1.19)	77.74(1.63)	79.00(1.72)	73.13(1.17)	69.28(1.19)	66.76(0.93)	59.63(0.71)
4.0	84.13(1.34)	85.64(1.58)	82.81(1.81)	84.71(1.11)	81.13(2.03)	80.23(1.92)	77.71(1.04)	70.63(1.06)
6.0	92.17(0.99)	94.97(0.71)	92.91(1.63)	92.71(1.38)	89.37(1.19)	89.71(0.98)	85.81(0.99)	86.62(1.61)
8.0	98.71(2.63)	99.71(1.07)	99.32(0.32)	97.71(1.28)	96.71(1.03)	97.63(0.88)	95.92(1.01)	98.93(1.09)
`K' value (%)	31.62	25.48	25.88	27.19	24.78	22.17	22.45	23.78
`n'	0.74415	0.75292	0.75141	0.75080	0.74729	0.74873	0.74265	0.73325

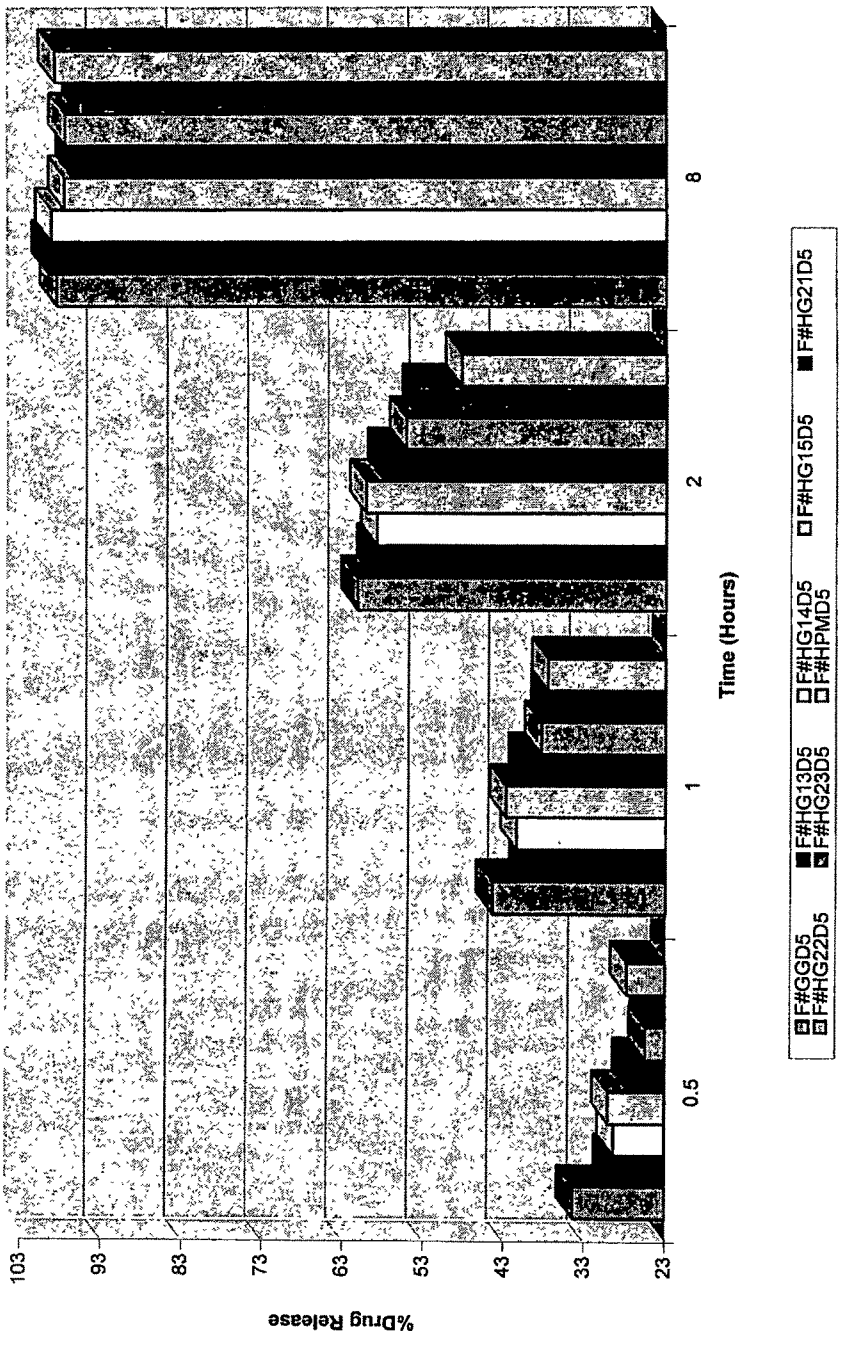


Fig 5.4.2 B Effect of hydrolysis of GG on release of DIL.

Table 5.4.3A Effect of Methylation of GG on Release of CPM from MGG matrices.

Time(Hours)	Cumulative % drug Release(S.E.)				
	F#GGC5	F#MG1C5	F#MG2C5	F#MG3C5	F#HPMC5
0.0	0.00	0.00	0.00	0.00	0.00
0.5	37.06(2.13)	30.55(1.60)	30.11(1.05)	25.46(0.51)	29.31(0.99)
1.0	48.32(2.93)	45.65(0.71)	42.76(1.39)	40.58(0.07)	40.58(0.07)
2.0	63.29(1.68)	62.05(0.51)	60.28(0.96)	51.25(0.17)	51.25(0.17)
3.0	75.56(1.02)	79.44(1.17)	71.48(0.65)	62.91(0.53)	62.99(0.53)
4.0	82.91(1.63)	83.22(0.61)	84.85(0.38)	72.85(0.60)	72.85(0.60)
6.0	86.41(1.17)	91.77(0.63)	92.97(0.77)	82.70(0.42)	82.70(0.42)
8.0	89.93(0.79)	96.80(0.84)	99.93(0.73)	94.35(0.76)	94.36(0.76)
`K' value(%)	39.28	29.17	26.96	21.25	27.33
`n'	0.731428	0.74845	0.74939	0.74746	0.72861

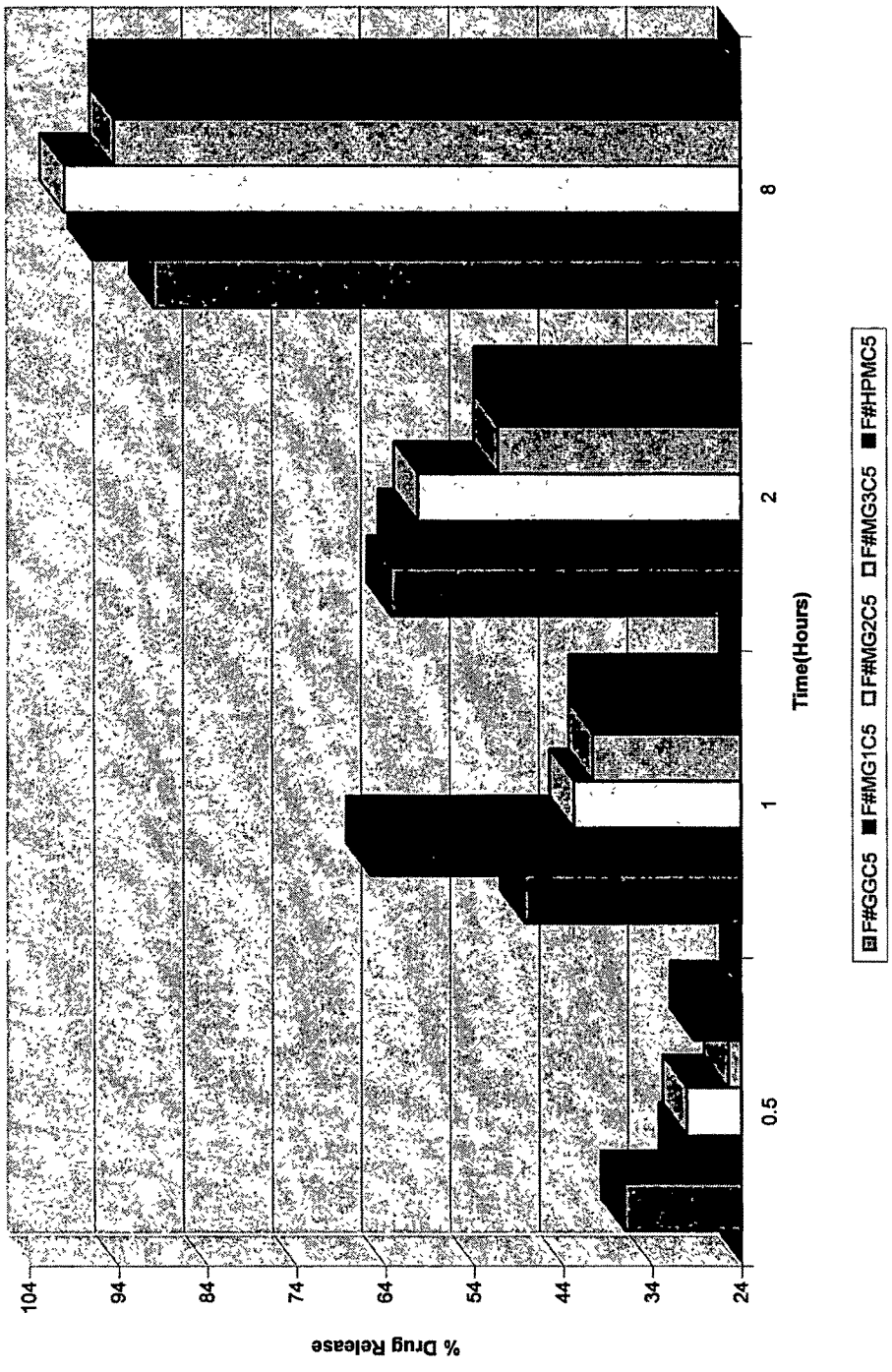


Fig 5.4.3 A Effect of methylation of GG on release of CPM

Table 5.4.3B Effect of Methylation of GG on Release of DIL from MGG matrices.

Time(Hours)	Cumulative % drug Release(S.E.)				
	F#GGD5	F#MG1D5	F#MG2D5	F#MG3D5	F#HPMD5
0.0	0.00	0.00	0.00	0.00	0.00
0.5	34.32 (2.44)	30.54(1.61)	29.28(1.06)	25.71(1.12)	29.31(0.99)
1.0	44.45 (2.03)	42.42(0.91)	42.63(2.01)	36.91(1.03)	40.58(0.07)
2.0	61.32(1.72)	62.72(1.06)	59.66(1.11)	52.38(1.47)	51.25(0.17)
3.0	74.23(1.09)	76.43(1.17)	75.56(1.03)	68.66(0.93)	62.99(0.53)
4.0	84.13(1.34)	86.63(0.97)	84.85(0.63)	80.23(0.77)	72.85(0.60)
6.0	92.17(0.99)	94.77(0.89)	92.97(0.72)	90.23(0.69)	82.70(0.42)
8.0	98.71(2.63)	99.94(0.84)	99.93(0.71)	98.92(1.42)	94.36(0.76)
`K' value(%)	31.62	26.92	26.16	21.56	27.33
`n'	0.74415	0.75293	0.75189	0.72785	0.72861

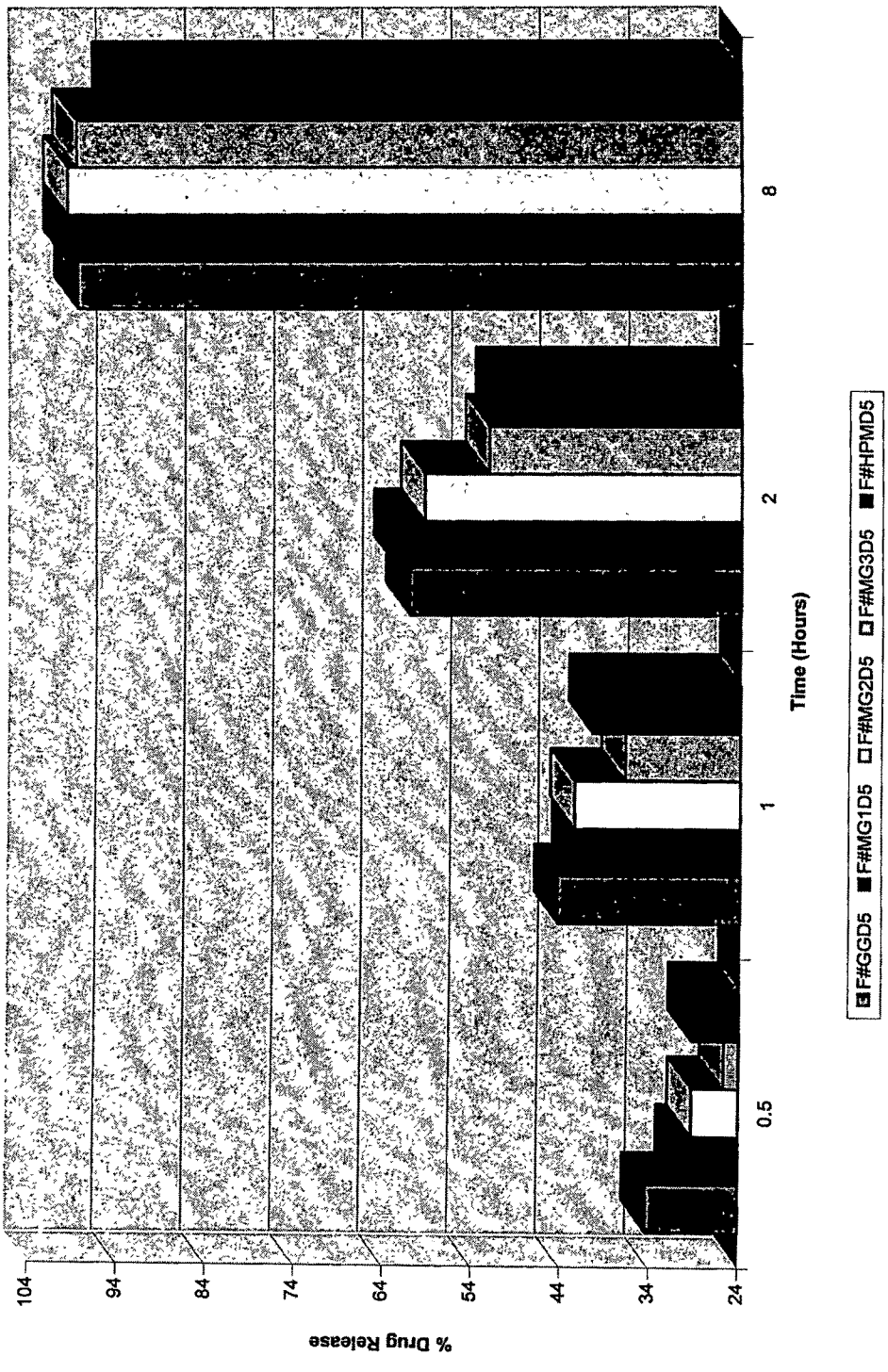


Fig 5.4.3B Effect of methylation of GG on release of DIL.

matrix and also diffusion of drug release decreases with time because of the strong and cohesive gel layer.

HGG and MGG matrix tablet formulations show reduction in the drug release in first half hour and one hour compared to GG (Table 5.4.2 and 5.4.3). A comparison of drug release in first two hours from GG and HGG matrices and GG and MGG matrices are shown in Fig 5.4.2 and 5.4.3 respectively. The release profiles are compared to that of HPMC matrix tablets. A significant reduction in the burst effect is observed on partial acid hydrolysis and methylation of GG as can be seen in the `k' values (Table5.4.2A, 5.4.2B, and 5.4.3A, 5.4.3B). It can be seen that the rate of drug release increases on modification. This may be due to reduction in polymer chain length on modification. The values of `n' suggest a non-Fickian anomalous diffusion mechanism of drug release from GG, HGG and MGG matrices.

5.7.3.3 Effect of composition of matrix on drug release :

The effect of water soluble/insoluble excipients in matrix was studied by varying the composition of the matrix as shown in Table 5.1.1 and 5.1.2. The composition of matrix was varied using lactose, microcrystalline cellulose and dibasic calcium phosphate, either alone or in combination and the drug release profile studied (Table 5.4.4.1 to 5.4.4.3). In case of formulations of matrix containing MCC as the diluent, the amount of drug release in half hour was 43.41% ± 2.77 and in one hour was 57.71% ± 2.71 from GG matrices, which is relatively higher than the amount of drug released in same time from formulation with lactose alone (37.06% ± 2.13 - 0.5h ; 48.32% ± 2.93 - 1.0h). It was observed that the values of drug released in initial half hour and one hour from HGG and MGG matrices with MCC as diluent were higher as compared to HGG and MGG matrices with lactose alone as a diluent. The distribution of MCC in the matrix leads to formation

Table 5.4.4.1A Effect of Diluents on Release of CPM from GG matrices.

Time(Hours)	Cumulative % drug Release(S.E.)				
	F#GGC5	F#GGC7	F#GGC8	F#GGC9	F#GGC10
0.0	0.00	0.00	0.00	0.00	0.00
0.5	37.06(2.13)	41.06(2.15)	43.41(2.77)	34.41(2.45)	35.31(2.51)
1.0	48.32(2.93)	51.34(1.66)	57.71(2.77)	45.46(2.21)	46.71(2.17)
2.0	63.29(1.68)	65.29(1.71)	69.38(1.96)	62.37(2.37)	62.29(1.26)
3.0	75.56(1.02)	80.56(1.08)	85.72(1.58)	75.31(1.35)	77.71(1.17)
4.0	82.91(1.63)	85.91(0.85)	88.72(1.58)	85.73(1.87)	85.76(1.89)
6.0	86.41(1.17)	88.41(0.73)	90.91(0.77)	92.39(0.92)	90.91(1.07)
8.0	89.93(0.79)	91.12(0.68)	91.93(0.67)	96.72(0.67)	93.33(1.39)
`K' value(%)	39.28	44.49	50.48	32.46	34.78
`n'	0.731428	0.73310	0.73605	0.74410	0.74083

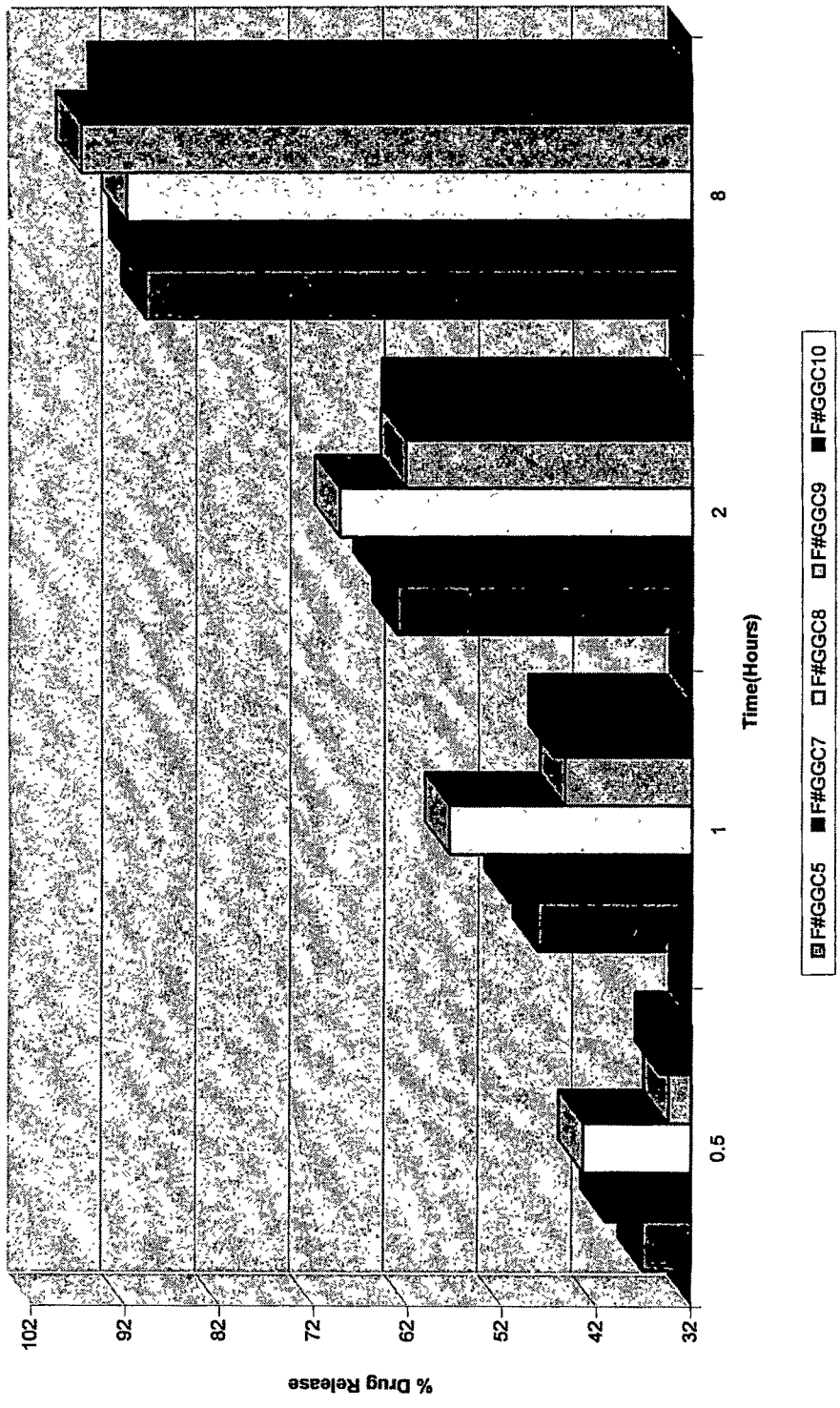


Fig 5.4.4.1 A Effect of diluents on release of CPM from GG matrices.

Table 5.4.4.1B Effect of Diluents on Release of DIL from GG matrices.

Time(Hours)	Cumulative % drug Release(S.E.)				
	F#GGD5	F#GGD7	F#GGD8	F#GGD9	F#GGD10
0.0	0.00	0.00	0.00	0.00	0.00
0.5	34.32 (2.44)	34.51(1.46)	32.31(1.47)	35.68(2.15)	37.71(2.73)
1.0	44.45 (2.03)	42.44(2.04)	40.42(2.04)	46.71(2.36)	48.31(2.04)
2.0	61.32(1.72)	58.61(1.07)	55.32(2.13)	62.97(1.11)	65.61(1.93)
3.0	74.23(1.09)	72.34(1.09)	69.38(1.93)	76.37(1.27)	77.71(1.23)
4.0	84.13(1.34)	84.14(0.89)	81.13(1.19)	84.12(1.48)	83.83(1.09)
6.0	92.17(0.99)	94.91(1.13)	91.93(1.02)	89.97(1.19)	88.37(1.16)
8.0	98.71(2.63)	99.92(1.29)	99.37(0.92)	92.97(1.11)	91.92(0.76)
`K' value(%)	31.62	28.09	27.82	35.50	39.23
`n'	0.74415	0.74488	0.74258	0.73831	0.73529

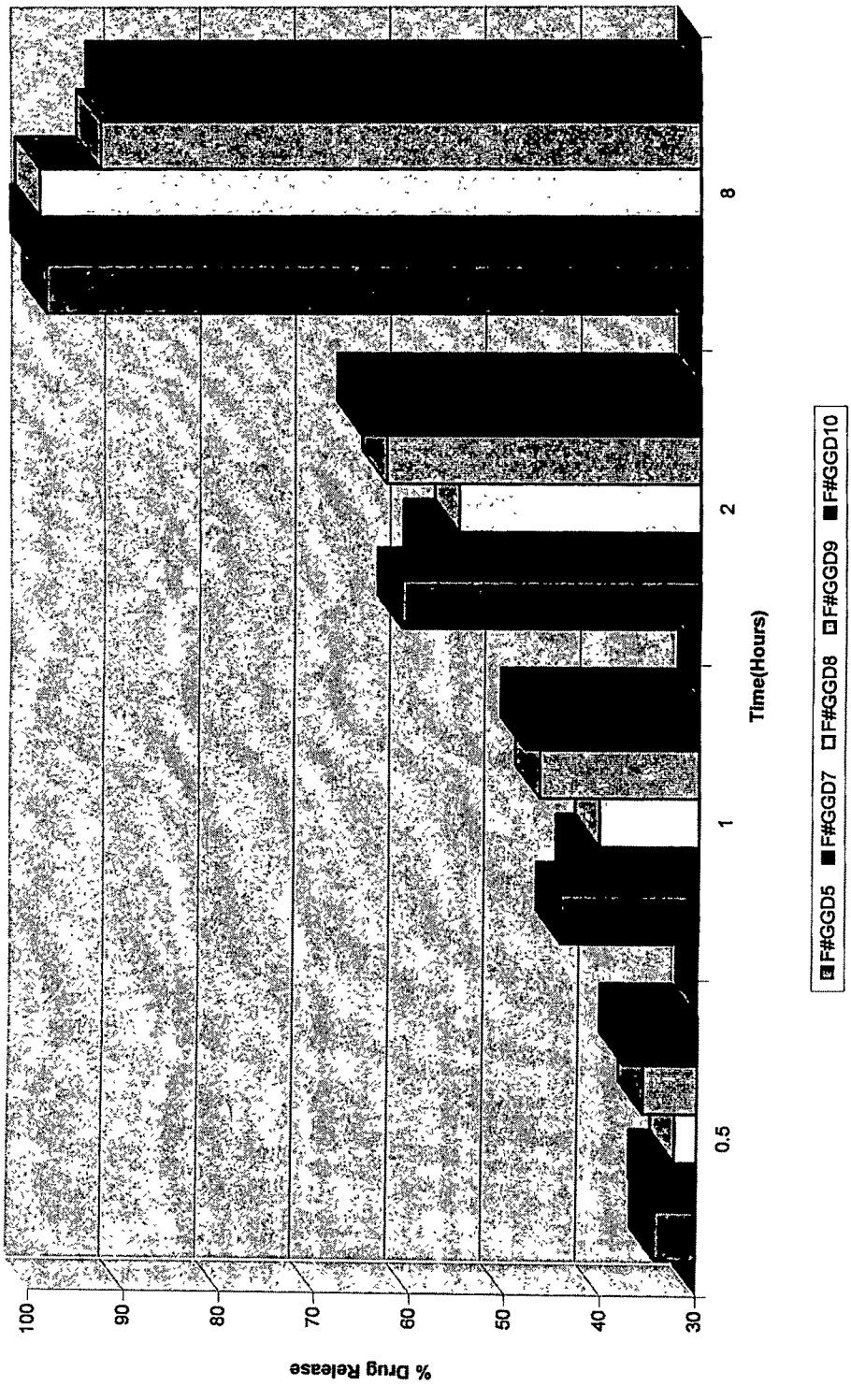


Fig 5.4.1 B Effect of diluents on release of DIL from GG matrices.

Table 5.4.4.2A Effect of Diluents on Release of CPM from HGG matrices.

Time(Hours)	Cumulative % drug Release(S.E.)				
	F#HG23C5	F#HG23C7	F#HG23C8	F#HG23C9	F#HG23C10
0.0	0.00	0.00	0.00	0.00	0.00
0.5	25.65 (1.25)	29.71(2.29)	31.73(2.31)	34.41(2.45)	35.51(2.51)
1.0	39.81 (0.96)	42.43(1.24)	44.71(2.01)	45.46(2.21)	46.71(2.17)
2.0	53.73(0.54)	59.38(1.95)	61.74(1.32)	62.37(1.43)	62.29(1.16)
3.0	65.55(0.34)	73.32(1.49)	72.71(0.77)	75.31(1.35)	77.71(1.43)
4.0	75.68(1.76)	84.71(1.48)	81.63(0.86)	85.73(1.77)	85.73(1.59)
6.0	83.72(1.11)	90.91(0.69)	86.81(1.73)	92.39(0.83)	91.91(1.08)
8.0	90.33(0.74)	93.47(0.39)	90.39(0.93)	96.72(1.49)	93.33(1.49)
`K' value(%)	24.46	27.60	31.82	32.46	34.91
`n'	0.73472	0.74486	0.73619	0.74407	0.74040

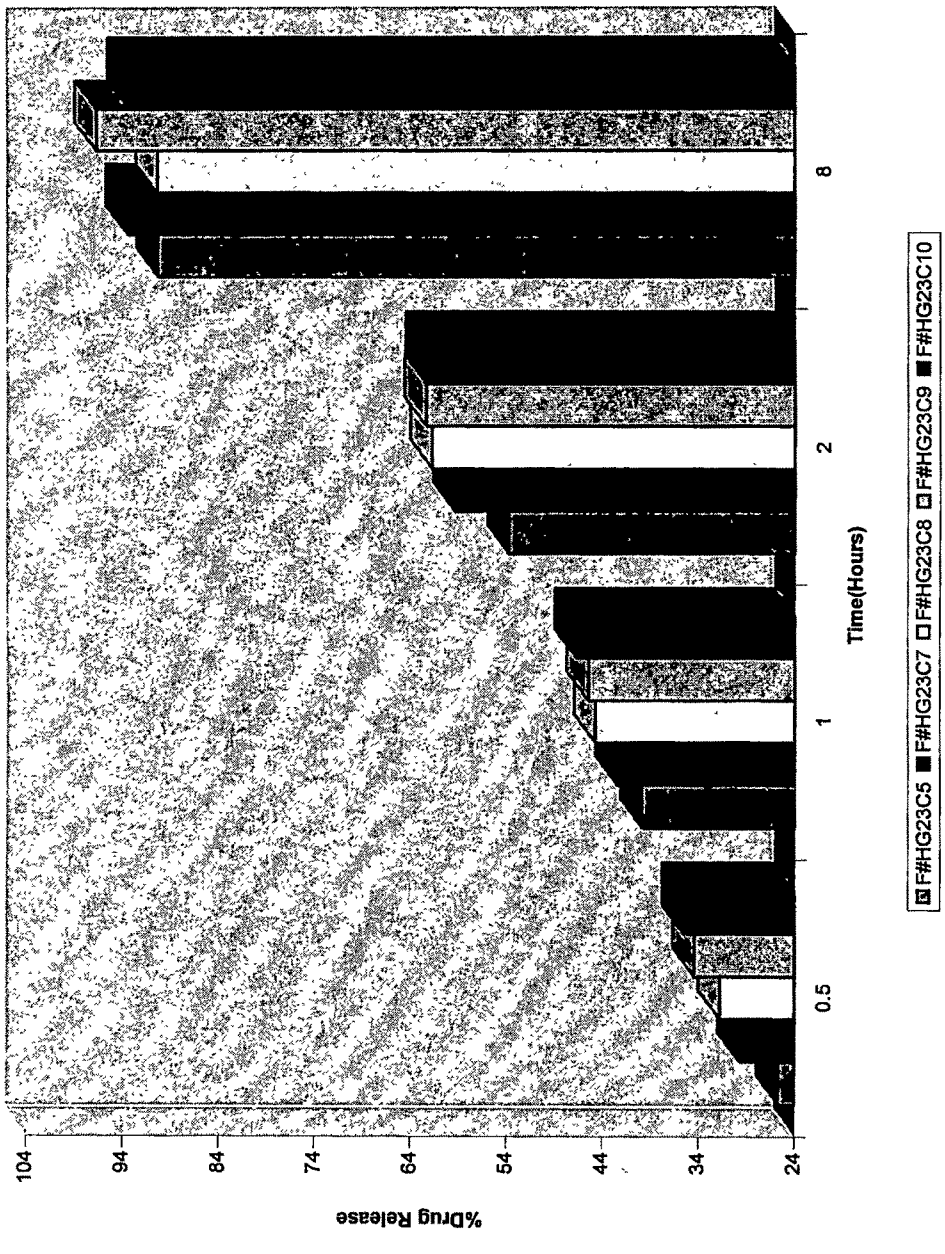


Fig 5.4.4.2 A Effect of diluents on release of CPM from HGG matrices.

Table 5.4.4.2B Effect of Diluents on Release of DIL from HGG matrices.

Time(Hours)	Cumulative % drug Release(S.E.)				
	F#HG23D5	F#HG23D7	F#HG23D8	F#HG23D9	F#HG23D10
0.0	0.00	0.00	0.00	0.00	0.00
0.5	25.25 (1.38)	25.31(1.63)	26.07(1.02)	28.13(1.82)	29.71(2.03)
1.0	37.71 (1.38)	36.61(1.06)	36.11(1.17)	39.91(2.19)	40.44(2.02)
2.0	53.76(1.09)	51.52(1.12)	51.23(1.32)	54.45(1.63)	55.71(1.67)
3.0	66.76(0.93)	63.67(1.32)	64.43(0.69)	65.71(1.45)	68.63(1.86)
4.0	77.71(1.04)	75.49(1.63)	77.63(0.79)	75.31(1.45)	78.43(1.14)
6.0	85.81(0.99)	86.63(1.01)	89.68(1.02)	83.49(1.98)	86.43(1.63)
8.0	95.92(0.79)	96.91(1.03)	97.98(0.88)	90.47(0.71)	92.44(0.69)
`K' value(%)	22.45	21.90	24.46	26.69	27.56
`n'	0.74265	0.74088	0.74395	0.73148	0.73593

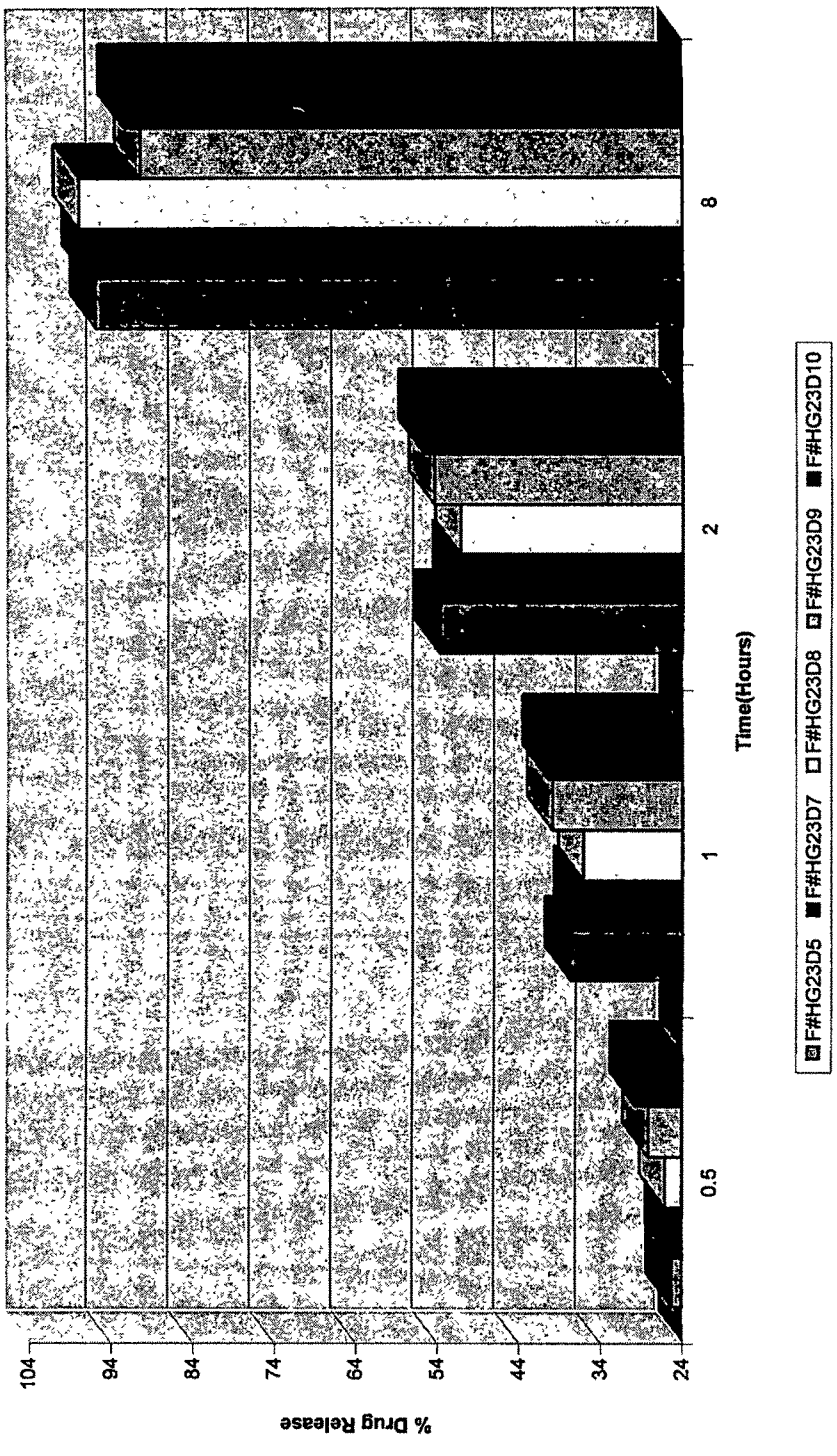


Fig 5.4.4.2B Effect of diluents on release of DIL from HGG matrices.

Table 5.4.4.3A Effect of Diluents on Release of CPM from MGG matrices.

Time(Hours)	Cumulative % drug Release(S.E.)				
	F#MG3C5	F#MG3C7	F#MG3C8	F#MG3C9	F#MG3C10
0.0	0.00	0.00	0.00	0.00	0.00
0.5	25.46(0.51)	29.14(1.77)	31.12(1.21)	24.51(1.52)	23.43(1.42)
1.0	35.48 (1.11)	47.17(1.02)	49.21(1.94)	35.31(1.35)	31.12(1.31)
2.0	54.36(1.47)	66.78(2.12)	69.23(1.26)	53.31(2.01)	52.33(2.05)
3.0	66.32(0.93)	74.58(2.14)	75.63(0.79)	65.49(0.69)	67.71(1.76)
4.0	78.13(0.66)	80.63(0.99)	80.11(0.91)	78.21(1.87)	80.24(1.08)
6.0	90.71(0.74)	87.16(0.99)	85.71(0.72)	91.22(0.77)	92.12(0.78)
8.0	97.74(1.47)	92.32(1.45)	88.41(0.89)	99.92(1.93)	98.19(0.89)
`K' value(%)	21.25	30.72	34.55	20.25	18.27
`n'	0.74746	0.74126	0.73587	0.74991	0.75391

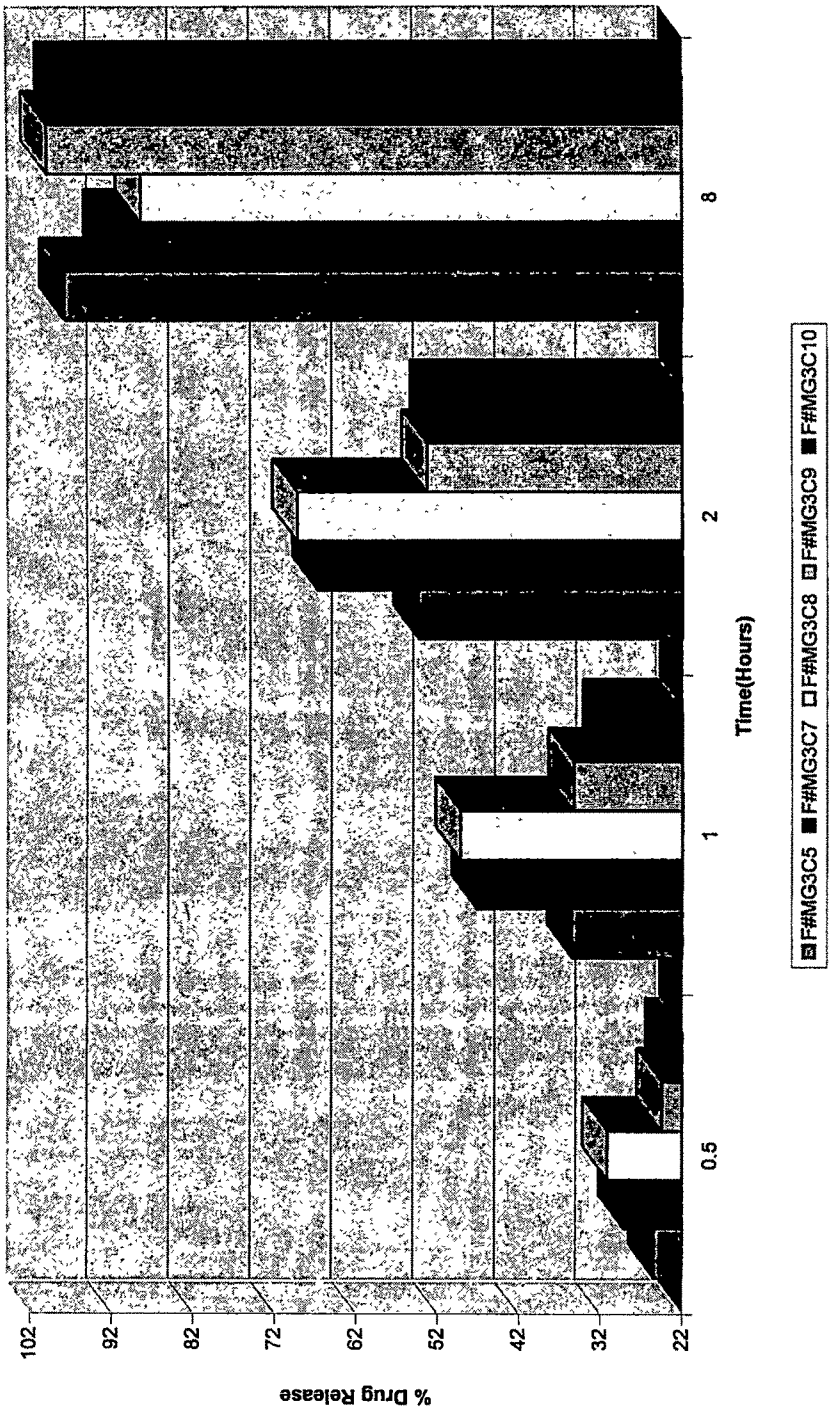


Fig 5.4.4.3 A Effect of diluents on release of CPM form MGG matrices.

Table 5.4.4.3B Effect of Diluents on Release of DIL from MGG matrices.

Time(Hours)	Cumulative % drug Release(S.E.)				
	F#MG3D5	F#MG3D7	F#MG3D8	F#MG3D9	F#MG3C10
0.0	0.00	0.00	0.00	0.00	0.00
0.5	25.71(1.12)	23.21(1.14)	23.03(0.71)	26.09(2.04)	28.13(2.11)
1.0	36.91 1.031)	34.28(1.37)	33.13(1.05)	36.11(2.03)	39.63(2.19)
2.0	52.38(1.47)	51.43(1.03)	49.27(1.15)	51.23(1.32)	54.78(1.91)
3.0	68.66(0.93)	66.71(1.33)	63.36(1.93)	64.57(1.28)	65.63(1.66)
4.0	88.23(0.77)	80.23(0.89)	77.71(0.88)	75.93(0.95)	74.71(1.03)
6.0	90.72(0.69)	91.38(0.98)	90.42(0.83)	85.23(0.99)	83.43(0.69)
8.0	98.92(1.47)	99.73(0.57)	99.69(1.01)	94.31(0.66)	90.43(1.22)
`K' value(%)	20.89	18.88	18.47	22.70	26.69
`n'	0.75275	0.75313	0.74973	0.73787	0.73122

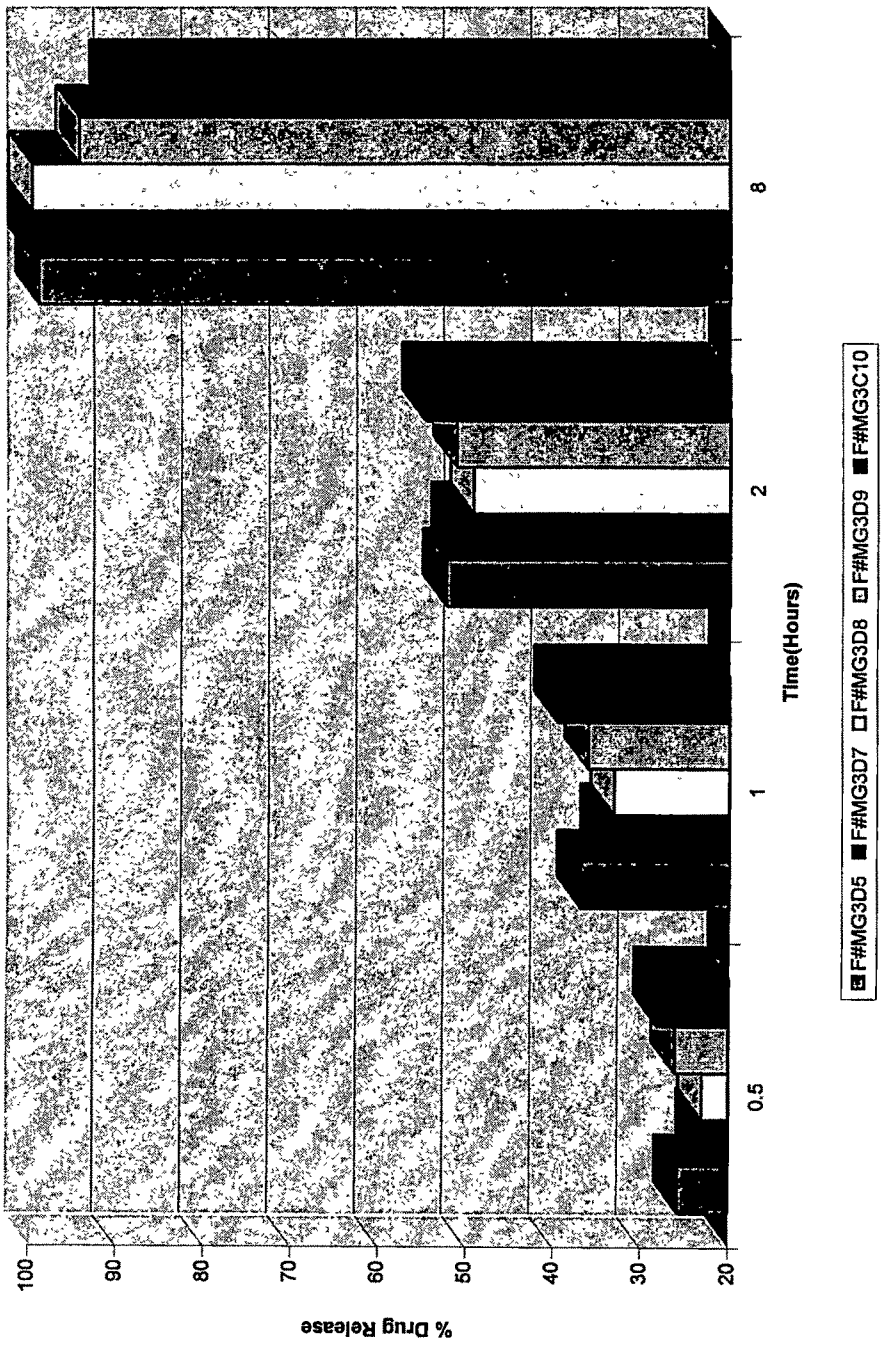


Fig 5.4.4.3 B Effect of diluents on release of DIL from MGG matrices.

of a porous structure. The hydrophilicity and water-insolubility of MCC results in more water penetrating into the porous tablet structure. This coupled with poor interaction coefficient and poor rate of hydration of GG cause an increased amount of drug release in initial hours. The hydrophobicity of DCP, when used as diluent in HGG and MGG matrices, may be the reason for reduction in the burst effect.

5.7.3.4 Effect of method of preparation on drug Release from GG/HGG/MGG matrices :

Formulation F#GGC5, F#HG23C5 and F#MG3C5 and F#GGD5, F#HG23D5 and F#MG3D5 were prepared by direct compression and wet granulation techniques (non-aqueous granulation) to study the effect of method of preparation on drug release profile. Mean cumulative percent drug release (alongwith standard error values) with respect to time are recorded in Table 5.4.5A and 5.4.5B and a comparative evaluation of drug release shown graphically in Fig 5.4.5A and 5.4.5B.

Results reveal that the amount of drug released from matrices, prepared by direct compression, in initial half and one hours is higher than that released from matrix prepared by wet granulation technique. The burst effect is higher in case of GG matrices (about 10 % higher) compared to HGG matrices (about 4 % higher) and MGG matrices (about 7% higher). The rate of drug release decreases with time once complete gelling of the matrix has taken place. This behaviour is also reflected in the `k' values (Table 5.4.4) and may be explained by the fact that PVP shows better binding properties when used as solution (in IPA) than being used as dry binder. This imparts stronger cohesion between particles (granules) in the matrix tablets, compared to the matrix tablets made by direct compression. Hence less amount of water enters into the tablets surface and dissolves the drug in the vicinity,which gets released. This results in lower drug release from

Table 5.4.5A Effect of Method of Preparation on Release of CPM from GG/HGG/MGG matrices.

Time(Hours)	Cumulative % drug Release(S.E.)					
	F#GGC5-d	F#GGC5-w	F#HG23C5-d	F#HG23C5-w	F#MG3C5-d	F#MG3C5-w
0.0	0.00	0.00	0.00	0.00	0.00	0.00
0.5	37.06(2.13)	27.51(2.68)	25.65(1.25)	22.24(2.73)	25.46(0.51)	18.77(0.66)
1.0	48.32(2.93)	42.35(2.63)	39.81(0.96)	35.42(1.09)	35.28(1.11)	30.34(0.51)
2.0	63.29(1.68)	53.90(1.01)	53.73(0.54)	48.75(1.32)	54.35(1.47)	45.69(0.43)
3.0	75.56(1.02)	62.82(1.41)	65.55(0.34)	60.77(0.81)	66.32(0.93)	61.48(0.74)
4.0	82.91(1.63)	70.28(1.73)	75.68(1.76)	71.28(1.73)	78.13(0.66)	78.28(1.02)
6.0	86.41(1.17)	79.23(0.64)	83.72(1.11)	82.23(0.64)	90.71(0.74)	89.97(0.91)
8.0	89.93(0.79)	85.68(0.86)	90.33(0.74)	90.68(0.86)	97.74(1.47)	96.37(1.48)
`K' value(%)	39.28	28.69	24.46	20.25	21.25	15.13
`n'	0.731428	0.73148	0.73472	0.73416	0.74746	0.75364

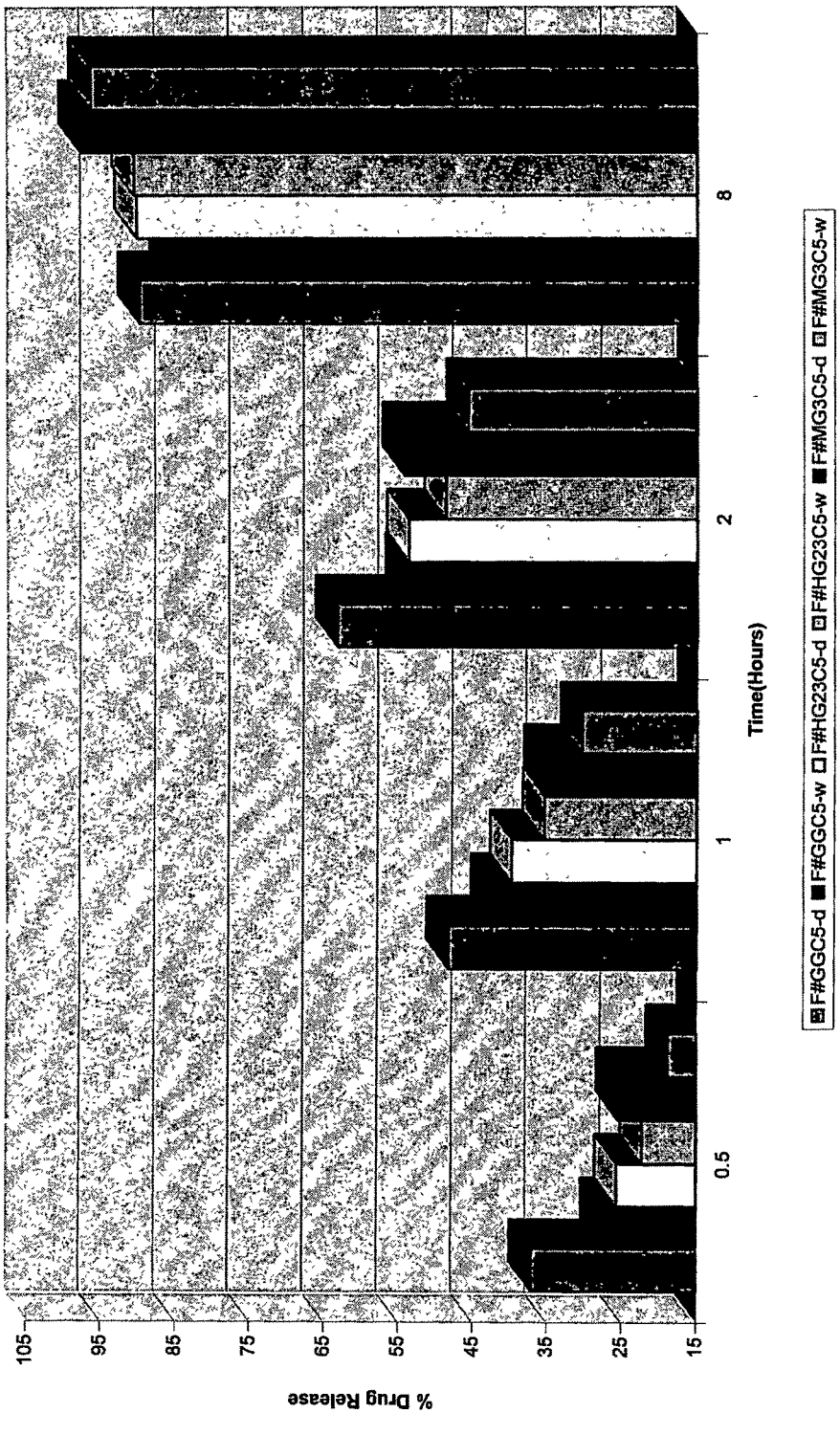


Fig 5.4.5 A Effect of method of preparation on release of CPM from GG/HGG/MGG matrices.

Table 5.4.5B Effect of Method of Preparation on Release of DIL from GG/HGG/MGG matrices.

Time(Hours)	Cumulative % drug Release(S.E.)					
	F#GGD5-d	F#GGD5-w	F#HG23D5-d	F#HG23D5-w	F#MG3D5-d	F#MG3D5-w
0.0	0.00	0.00	0.00	0.00	0.00	0.00
0.5	34.32(2.44)	25.48(2.63)	25.25(1.38)	21.19(2.31)	25.71(1.12)	18.68(1.11)
1.0	44.45(2.03)	40.49(2.11)	37.71(1.38)	33.47(1.71)	36.91(1.03)	30.31(1.43)
2.0	61.32(1.72)	53.78(1.93)	53.76(1.09)	47.63(1.79)	52.38(1.47)	45.71(0.41)
3.0	74.23(1.09)	64.63(1.48)	66.76(0.93)	60.68(1.27)	68.66(0.93)	59.71(0.88)
4.0	84.13(1.34)	73.71(1.09)	77.71(1.04)	73.71(1.34)	80.23(0.77)	75.75(1.02)
6.0	92.17(0.99)	80.19(0.71)	85.81(0.99)	83.94(1.46)	90.72(0.69)	88.63(0.91)
8.0	98.71(0.63)	85.72(0.69)	95.92(1.01)	92.29(1.47)	98.92(1.42)	98.93(0.76)
`K' value(%)	31.60	25.72	22.45	18.46	21.56	15.04
`n'	0.74415	0.72760	0.74266	0.73964	0.74897	0.75254

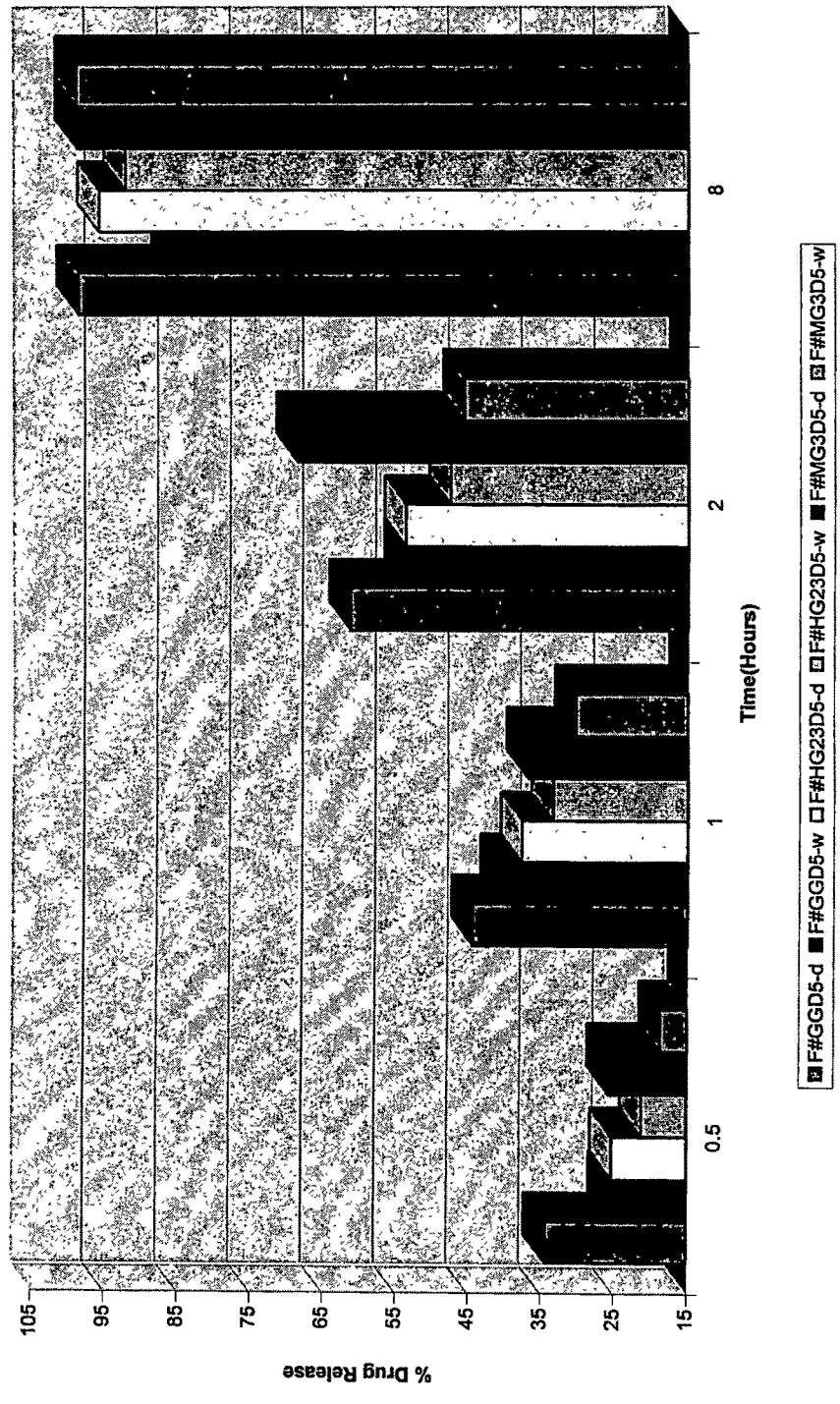


Fig 5.4.5 B Effect of method of preparation on release of DiL from GG/HGG/MGG matrices.

matrices prepared with wet granulation as compared to those prepared by direct compression. This phenomenon may also be attributed to faster hydration of gum on being activated using solvent whereby the installation of gel layer occurs rapidly and hence delays the drug release. The kinetic parameters show a non-Fickian anomalous diffusion mechanism of drug release.

5.7.3.5. Effect of pH of dissolution medium on drug Release :

Formulations F#GGC5, F#GGD5, F#HG23C5, F#HG23D5, F#MG3C5, and F#MG3D5 were subjected to dissolution medium of pH 1.2, 5.4, 6.8 and 7.4 to study the effect of change in pH of media on drug release profile. The results are recorded in Table 5.4.6.1 to 5.4.6.3 and comparison shown graphically in Figs 5.4.6.1 to 5.4.6.3.

It can be observed from the results that the burst effect seen with GG matrix is increased at pH 1.2. A significantly high amount of drug is released in initial half hour (30.43%±2.43) and one hour (49.71%±3.02) at pH 1.2 compared to that at pH 6.8 (0.5h - 27.51±2.68; 1.0h - 42.35%±2.63) and pH 7.4 (0.5h - 26.28%±2.77; 1.0h - 40.72%±1.71). The reason for such a phenomena may be attributed to poor rate of hydration of GG at low pH values. The maximum rate of hydration of GG has been reported at pH 5 to 7. No significant difference in the amount of drug release in initial half hour and one hour at pHs - 5.4, 6.8, and 7.4 is observed. The rate of drug release decreases with time.

A similar pattern of behavior at different pH is observed with HGG and MGG. The amount of drug released in initial half hour and one hour is higher at pH 1.2. Compared to GG, HGGs and MGGs show the effect of a pH to lower degree. The rank order correlation of the GG and Modified GG matrices with respect to the effect of pH on drug release may be shown as -

Table 5.4.6.1 A Effect of pH of dissolution medium on Release of CPM from GG matrices.

Time(Hours)	Cumulative % drug Release(S.E.) from F#GGC5 at			
	pH 1.2	pH 5.4	pH 6.8	pH 7.4
0.0	0.00	0.00	0.00	0.00
0.5	30.43(2.43)	29.71(2.43)	27.51(2.68)	26.28(2.77)
1.0	49.71(3.02)	45.65(2.45)	42.35(2.63)	40.72(1.71)
2.0	61.23(2.58)	55.72(1.75)	53.90(1.01)	53.71(1.35)
3.0	70.23(1.42)	65.32(1.36)	62.82(1.41)	64.22(1.27)
4.0	78.77(1.89)	71.67(1.71)	70.28(1.73)	70.12(0.91)
6.0	86.27(1.67)	83.68(1.87)	79.23(0.64)	82.74(1.02)
8.0	91.77(1.79)	90.27(0.79)	85.68(0.86)	90.13(0.87)
`K' value(%)	32.49	30.76	26.68	25.76
`n'	0.73466	0.72636	0.72106	0.72921

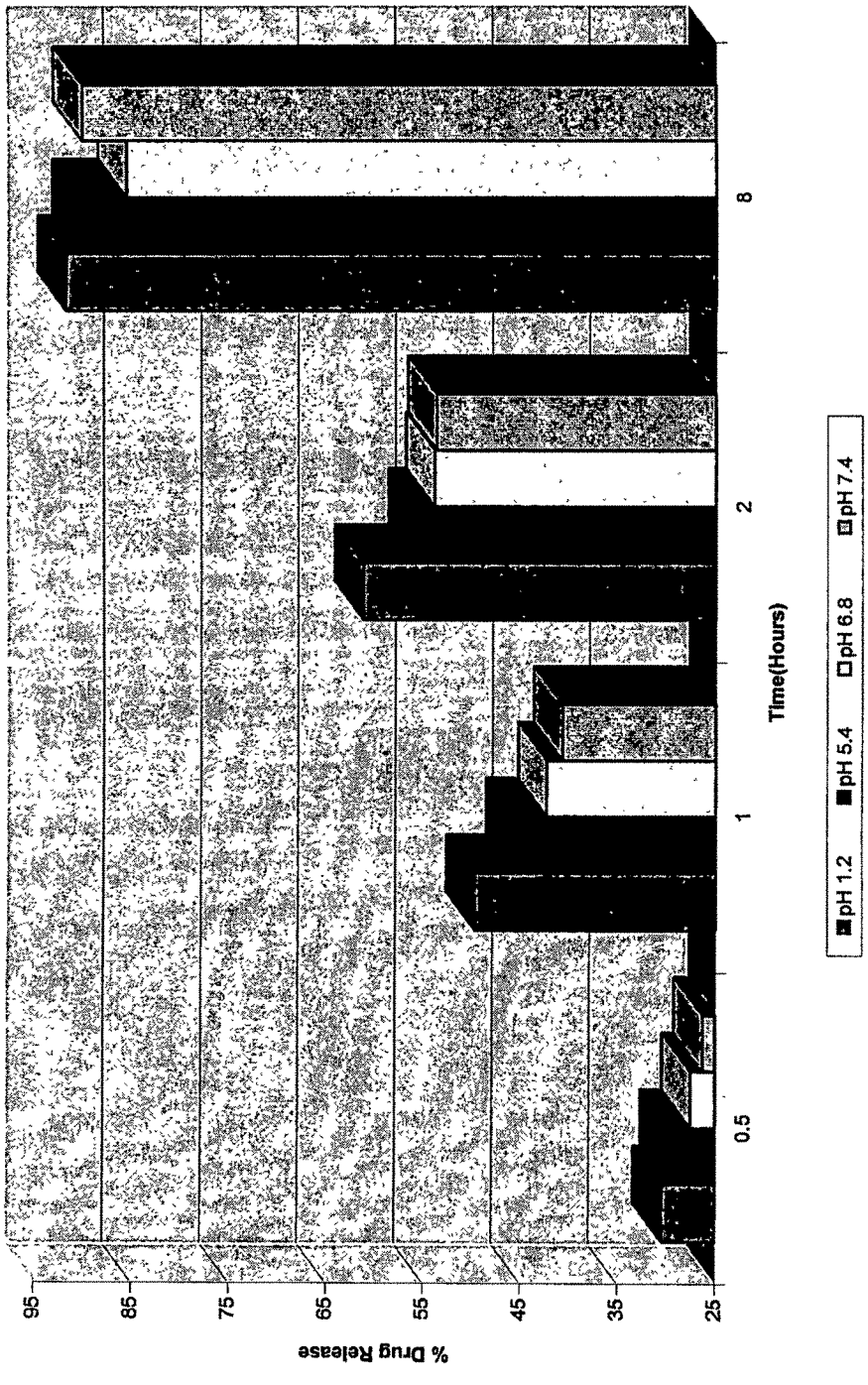


Fig 5.4.6.1 A Effect of pH of dissolution medium on release of CPM from GG matrices.

Table 5.4.6.1B Effect of pH of dissolution medium on Release of DIL from GG matrices.

Time(Hours)	Cumulative % drug Release(S.E.) from F#GGD5 at			
	pH 1.2	pH 5.4	pH 6.8	pH 7.4
0.0	0.00	0.00	0.00	0.00
0.5	38.09(2.66)	35.03(2.34)	34.32(2.41)	33.12(2.41)
1.0	47.93(2.94)	44.79(2.11)	44.45(2.03)	44.63(2.22)
2.0	65.67(1.93)	62.43(2.09)	61.32(1.72)	62.04(1.62)
3.0	77.73(1.69)	76.22(1.44)	74.23(1.09)	74.11(1.47)
4.0	88.36(1.58)	86.32(1.56)	84.13(1.34)	84.19(1.48)
6.0	94.96(1.46)	93.28(1.12)	92.17(0.99)	92.93(0.92)
8.0	99.22(1.03)	97.93(1.06)	98.71(1.63)	98.63(1.68)
`K' value(%)	36.31	32.36	31.62	30.62
`n'	0.74599	0.74556	0.74415	0.74591

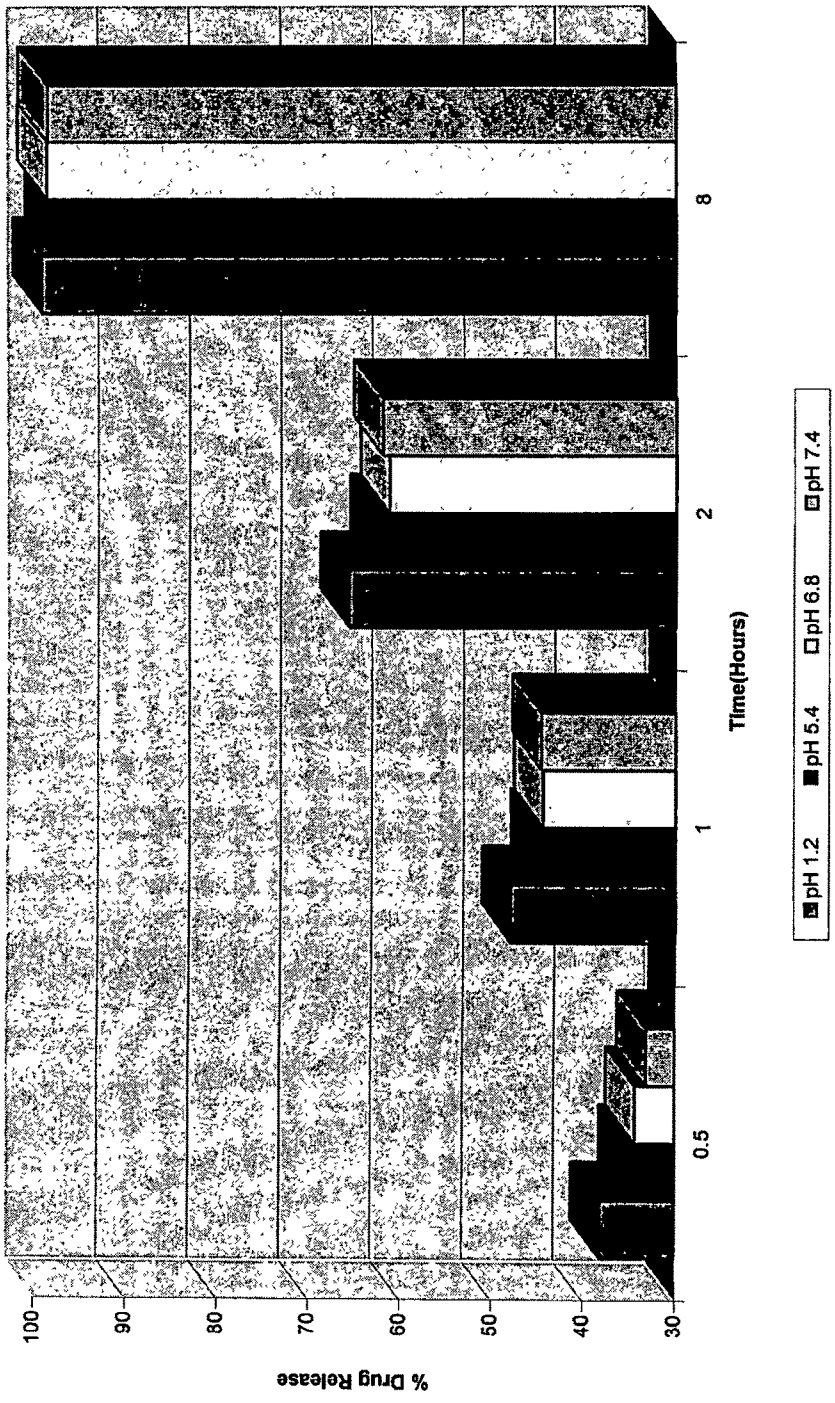


Fig 5.4.6.1 B Effect of pH of dissolution medium on release of DIL from GG matrices.

Table 5.4.6.2 A Effect of pH of dissolution medium on Release of CPM from HGG matrices.

Time(Hours)	Cumulative % drug Release(S.E.) from F#HG23C5 at			
	pH 1.2	pH 5.4	pH 6.8	pH 7.4
0.0	0.00	0.00	0.00	0.00
0.5	26.79(2.63)	25.51(2.19)	22.24(2.73)	21.27(2.72)
1.0	41.73(1.69)	40.71(1.18)	35.42(1.09)	36.73(2.41)
2.0	54.79(1.49)	52.17(1.35)	48.75(1.32)	47.63(1.74)
3.0	66.72(0.98)	62.82(1.19)	60.77(0.31)	61.32(1.43)
4.0	76.71(1.17)	70.28(0.96)	71.28(1.73)	72.71(0.98)
6.0	87.71(0.91)	83.72(0.98)	82.23(0.64)	82.29(0.77)
8.0	95.51(0.63)	90.33(0.71)	90.68(0.86)	89.63(0.36)
`K' value(%)	24.97	24.80	20.25	19.84
`n'	0.74020	0.73006	0.73416	0.73535

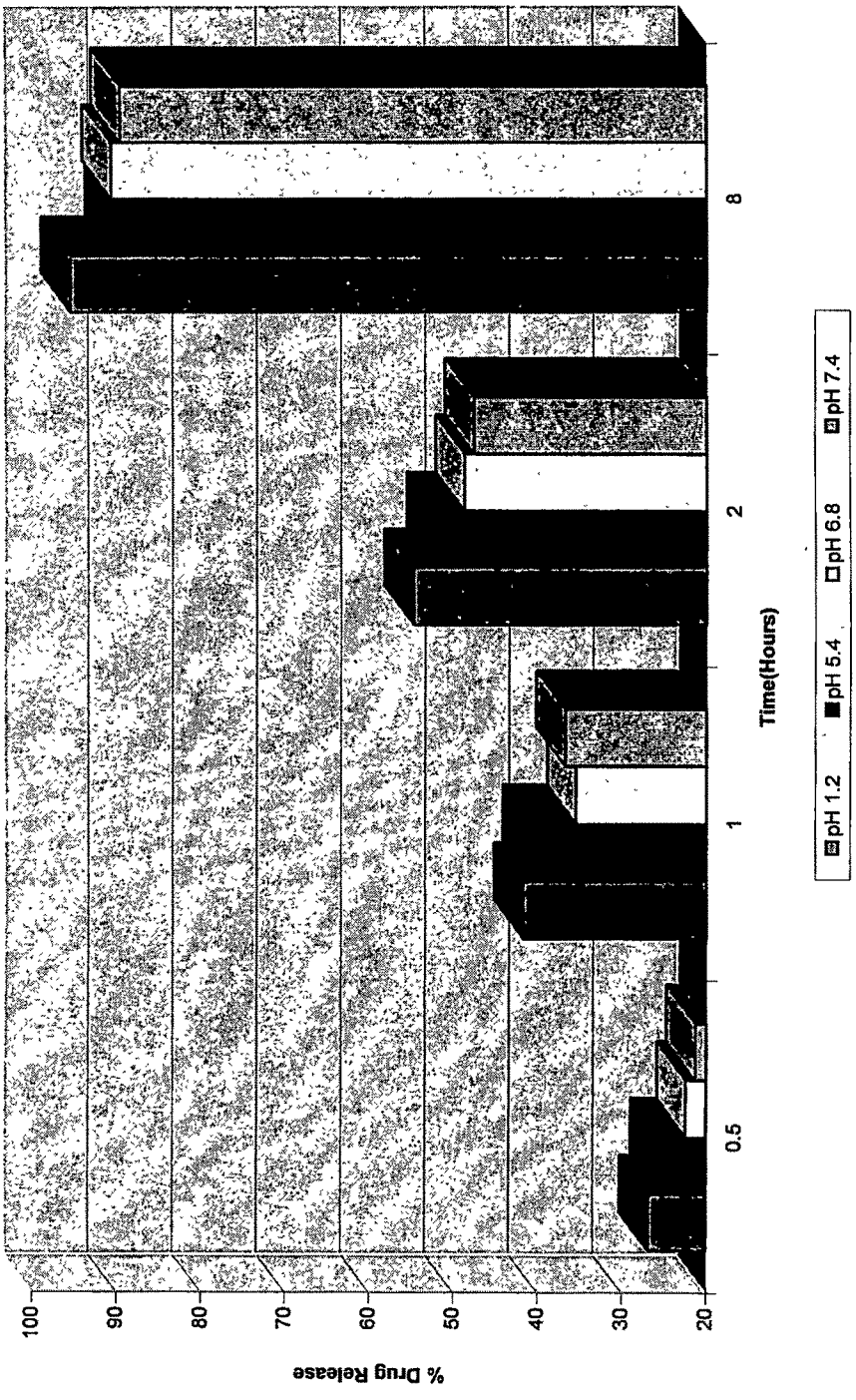


Fig 5.4.6.2 A Effect of pH of dissolution medium on release of CPM from HGG matrices.

Table 5.4.6.2 B Effect of pH of dissolution medium on Release of DIL from HGG matrices.

Time(Hours)	Cumulative % drug Release(S.E.) from F#HG23D5 at			
	pH 1.2	pH 5.4	pH 6.8	pH 7.4
0.0	0.00	0.00	0.00	0.00
0.5	29.29(2.07)	25.31(2.71)	25.25(1.38)	25.06(2.11)
1.0	41.44(2.11)	38.72(1.83)	37.71(1.38)	37.38(1.33)
2.0	58.90(1.43)	54.43(1.45)	53.26(1.09)	50.41(1.63)
3.0	77.74(1.63)	68.39(1.83)	67.76(0.93)	64.48(1.63)
4.0	82.81(1.81)	80.44(1.09)	77.71(1.04)	75.69(1.65)
6.0	92.21(1.63)	89.71(0.97)	85.81(0.99)	84.49(1.64)
8.0	99.32(0.71)	97.63(0.89)	95.92(1.01)	93.42(1.39)
`K' value(%)	25.9516	22.19	22.40	22.40
`n'	0.75100	0.74813	0.74296	0.73769

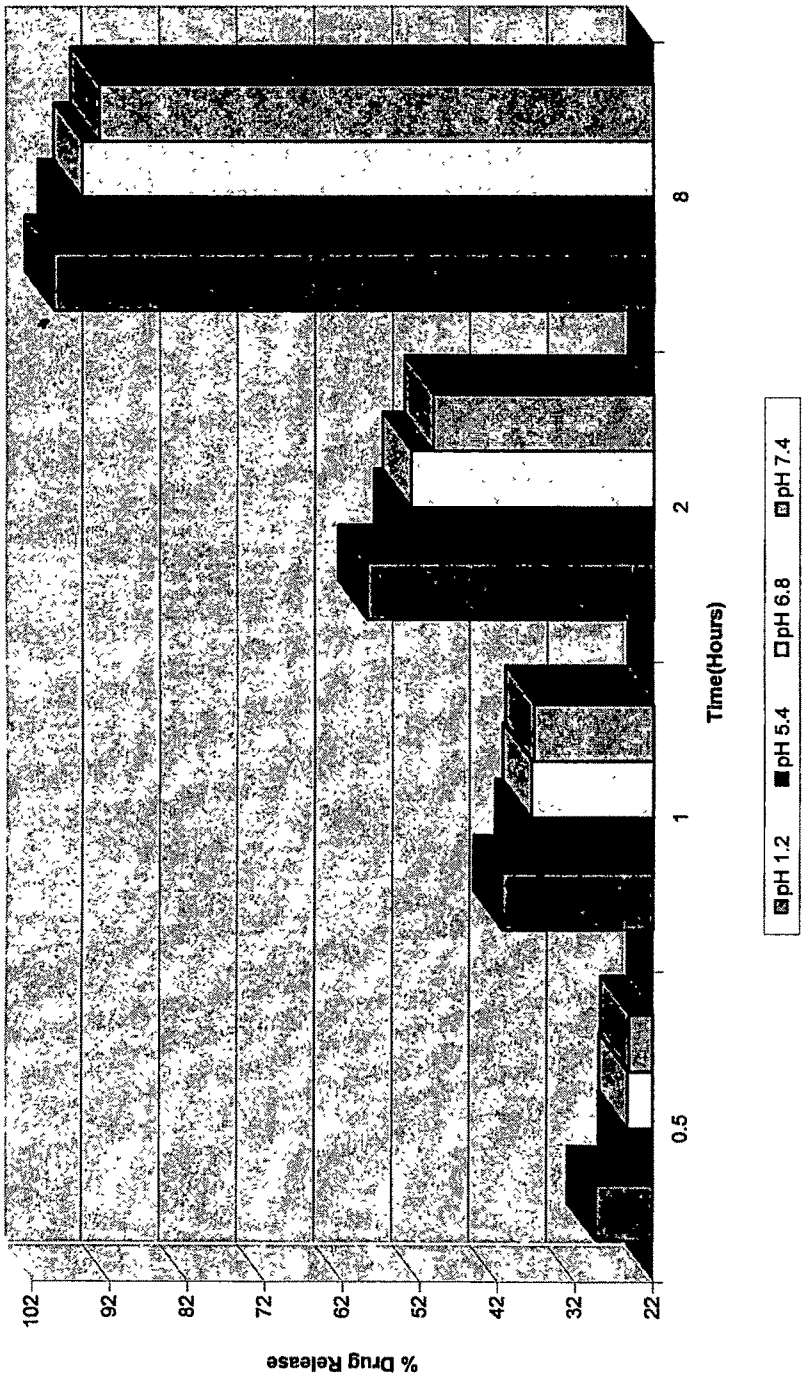


Fig 5.4.6.2 B Effect of pH of dissolution medium on release of DIL from HGG matrices.

Table 5.4.6.3 A Effect of pH of dissolution medium on Release of CPM from MGG matrices.

Time(Hours)	Cumulative % drug Release(S.E.) from F#MG3C5 at			
	pH 1.2	pH 5.4	pH 6.8	pH 7.4
0.0	0.00	0.00	0.00	0.00
0.5	21.23(1.11)	19.38(1.07)	18.77(0.66)	18.63(0.89)
1.0	31.38(1.13)	30.56(0.63)	30.34(0.51)	30.41(0.71)
2.0	45.71(0.64)	45.63(0.71)	45.69(0.43)	45.74(0.75)
3.0	62.39(0.99)	62.37(0.78)	61.48(0.74)	60.73(0.31)
4.0	77.63(1.11)	79.23(2.01)	78.28(1.02)	76.71(1.03)
6.0	89.71(1.33)	90.22(0.66)	89.97(0.91)	89.09(1.07)
8.0	97.71(0.73)	97.08(1.11)	96.37(1.48)	95.92(0.75)
`K' value(%)	16.84	15.46	15.13	15.18
`n'	0.74981	0.75395	0.75364	0.75188

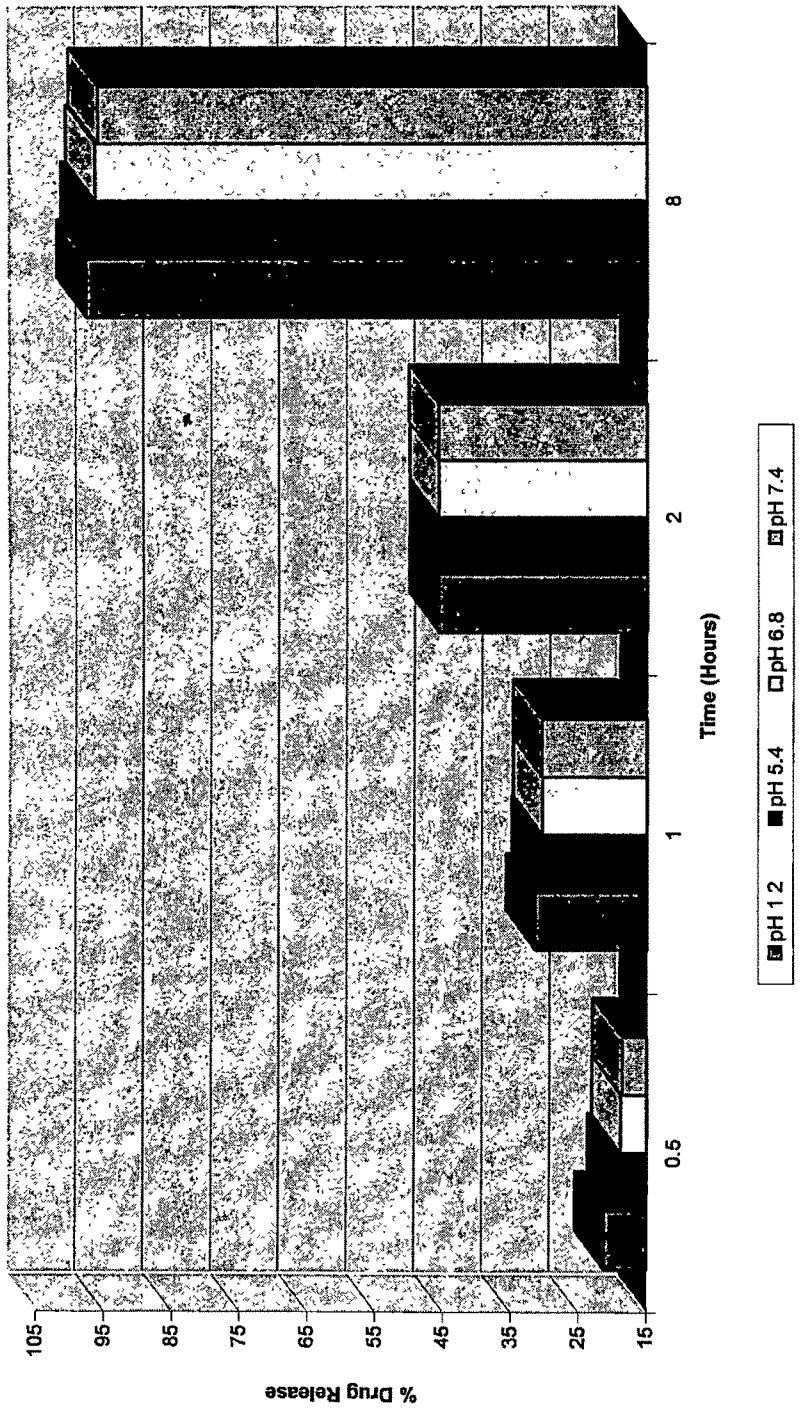


Fig 5.4.6.3 A Effect of pH of dissolution medium on release of CPM from MGG matrices.

Table 5.4.6.3 B Effect of pH of dissolution medium on Release of DIL from MGG matrices.

Time(Hours)	Cumulative % drug Release(S.E.) from F#MG3D5 at			
	pH 1.2	pH 5.4	pH 6.8	pH 7.4
0.0	0.00	0.00	0.00	0.00
0.5	29.28(1.06)	27.71(1.11)	25.71(1.12)	25.29(1.11)
1.0	42.63(2.03)	37.63(1.04)	36.71(1.03)	36.28(1.28)
2.0	59.66(2.22)	50.41(1.63)	52.38(1.47)	50.49(1.03)
3.0	73.48(1.93)	67.79(1.76)	68.66(0.93)	67.43(1.76)
4.0	83.98(1.04)	79.43(1.49)	80.23(0.77)	79.34(1.37)
6.0	92.43(1.29)	89.48(1.49)	90.72(0.69)	89.89(1.43)
8.0	99.43(1.02)	96.67(1.69)	98.92(1.42)	97.71(1.77)
`K' value(%)	26.34	23.50	21.50	21.16
`n'	0.75001	0.74256	0.74903	0.74691

Fig 5.4.6.3 B Effect of pH of dissolution medium on release of DIL from MGG matrices.

GG > HGG > MGG

The release kinetics determined using Ritgers' equation show that the release of drug from the matrices follow non-Fickian anomalous diffusion mechanism.

5.7.4. In Vivo Evaluation :

GG, HGG, MGG and HPMC matrix tablets were prepared by wet granulation technique using PPA as model drug, as per the composition shown in the Table 5.1.3. Swelling characteristics and gel strength of these matrix tablets were determined and recorded in Table 5.5.1. These matrix tablets were also checked for the *in vitro* drug dissolution profile. The results are recorded in Table 5.5.2 and shown graphically in Fig 5.5.1.

These matrix tablets were further evaluated for drug release *in vivo* using 12 healthy male human volunteers of age between 22 - 26 years and weighing between 55 - 70 kgs. The number of volunteers were divided into 4 groups of 3 volunteers each and the study was conducted by single dose complete crossover design. Each volunteer was administered one matrix (GG, HGG, MGG, HPMC) tablet containing 75 mg of PPA, with 200ml of water following overnight fast. Data of urinary excretion of drug over a period of 24 hours were recorded (Table 5.5.3 and Fig 5.5.2).

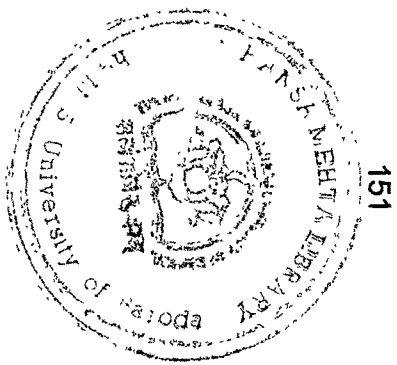
Results reveal that the amount of drug excreted from GG matrix tablets in initial hours (1h to 6h) is significantly high compared to that from HGG, MGG and HPMC matrices. About 40% of drug is excreted in 6h from GG matrices as compared to about 20% from HGG, MGG and HPMC matrices. This further confirms the burst effect observed in case of GG *in vitro*. It can be concluded from the profile of drug excreted in urine that the drug level is significantly prolonged in case of HGG, MGG and HPMC matrices as

Table 5.5.1 Swelling characteristics and Gel Strength of formulations with PPA as model drug.

Sr. No.	Formul. No.	Hydrogel	Surface area (sq mm) X 3.14 at Time (Hours)						Gel Strength (ml)
			0.0h	0.5h	1.0h	2.0h	4.0h	24.0h	
1.	P1	GG	20.26 (0.06)	58.50 (1.85)	78.15 (2.93)	97.51 (2.71)	117.50 (2.93)	122.20 (2.78)	40.27 (1.28)
2.	P2	HGG	20.11 (0.18)	53.24 (2.55)	74.12 (2.39)	90.60 (2.71)	112.24 (2.76)	129.00 (2.36)	36.32 (1.71)
3.	P3	MGG	20.17 (0.08)	36.73 (1.54)	55.73 (2.77)	66.73 (2.97)	80.98 (1.89)	87.41 (2.68)	27.61 (1.72)
4.	P4	HPMC	20.22 (0.07)	33.41 (1.72)	54.65 (2.65)	65.89 (2.61)	78.90 (1.98)	89.93 (2.63)	25.21 (1.22)

Table 5.5.2 Drug Release Profile from Matrix Tablets of PPA.

Sr. No.	Time (Hours)	Cumulative % Drug Release (S.E.)			
		F#P1	F#P2	F#P3	F#P4
1.	0.00	0.00	0.00	0.00	0.00
2.	0.50	25.68 (1.71)	21.15 (2.16)	18.98 (1.63)	20.73 (1.51)
3.	1.00	40.36 (2.34)	34.32 (1.46)	30.49 (0.97)	32.71 (1.32)
4.	2.00	52.91 (1.72)	49.37 (1.84)	46.71 (0.43)	44.68 (0.71)
5.	3.00	62.82 (1.41)	60.77 (0.81)	61.77 (0.98)	55.21 (1.65)
6.	4.00	70.28 (1.72)	71.57 (1.88)	79.32 (1.02)	66.38 (0.73)
7.	6.00	79.23 (0.71)	82.23 (0.97)	90.91 (0.77)	82.47 (1.24)
8.	8.00	85.63 (0.86)	90.68 (0.80)	97.71 (1.48)	94.71 (0.76)



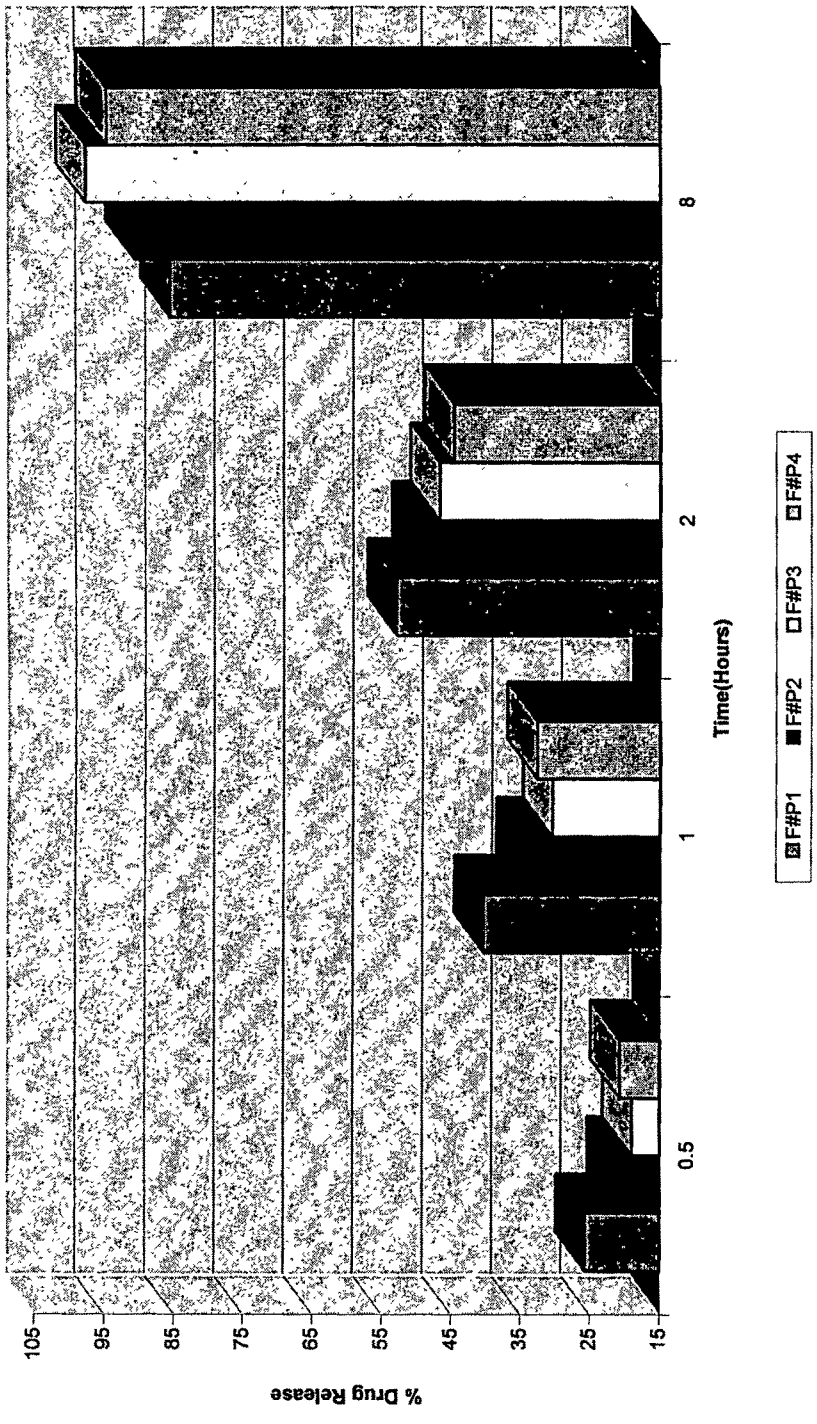


Fig. 5.5.1 Drug Release profile from matrix tablets of PPA.

Table 5.5.3 Urinary Excretion Data of PPA.

Sr. No.	Time (Hours)	Amount of PPA excreted in Urine from			
		F#P1 (mg)	F#P2 (mg)	F#P3 (mg)	F#P4 (mg)
1.	0	0	0	0	0
2.	1	4.32 ± 1.78	2.40 ± 0.89	1.67 ± 0.75	1.27 ± 0.77
3.	2	9.83 ± 2.46	3.72 ± 1.85	3.88 ± 2.45	3.87 ± 2.10
4.	4	9.26 ± 2.78	4.75 ± 2.05	4.87 ± 3.01	4.90 ± 1.09
5.	8	7.14 ± 2.64	5.57 ± 2.37	6.50 ± 3.11	7.20 ± 3.22
6.	12	4.17 ± 3.11	6.88 ± 3.31	7.14 ± 2.64	6.95 ± 2.17
7.	20	3.25 ± 2.79	5.85 ± 1.98	5.68 ± 2.43	5.79 ± 2.45
8.	24	1.75 ± 1.79	5.27 ± 2.75	4.85 ± 2.23	5.15 ± 2.56

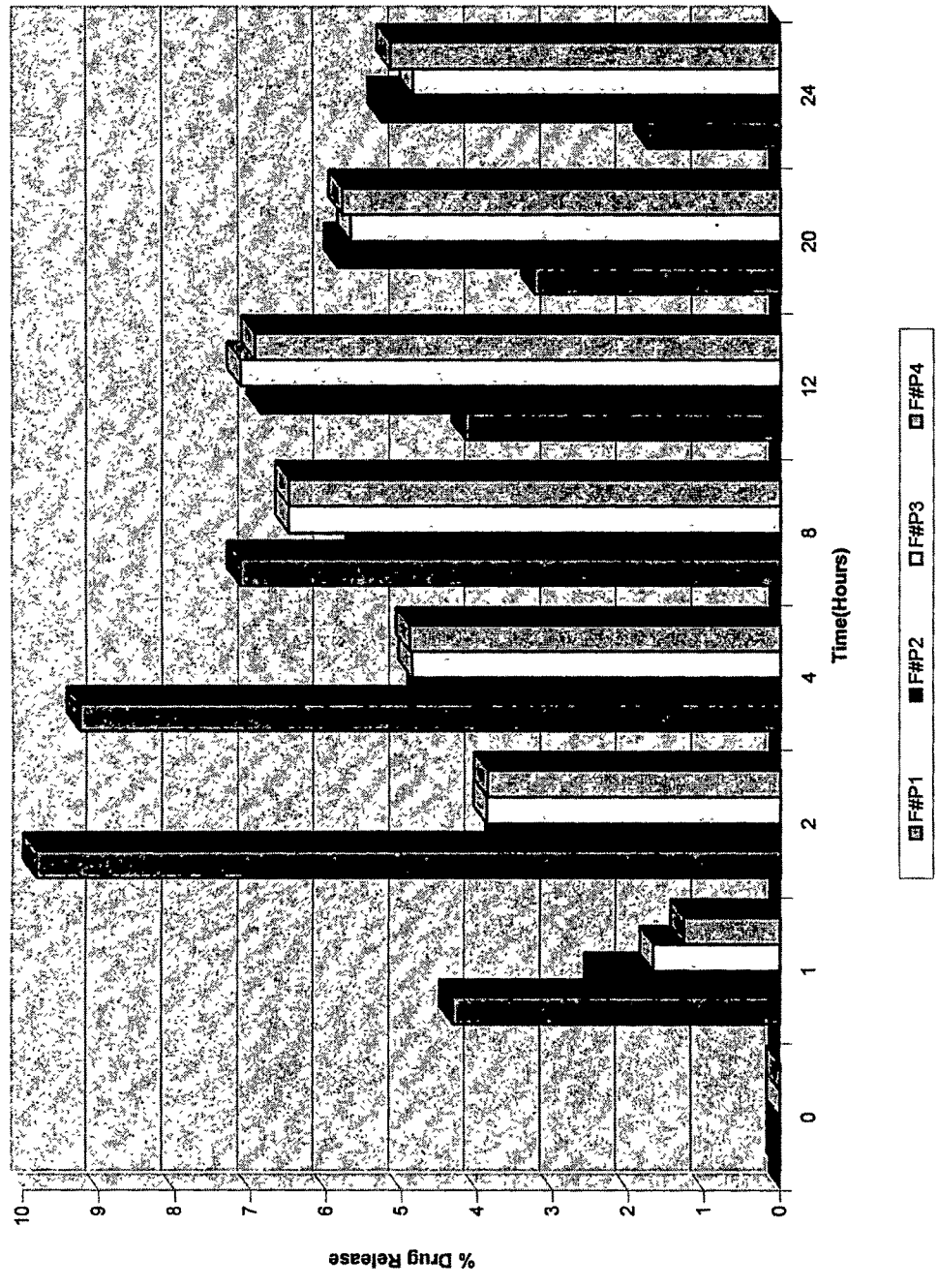


Fig 5.5.2 Urinary excretion of PPA.

compared to GG. The profiles of modified GGs (HGG, MGG) are similar to that observed for HPMC.

Thus it can be safely concluded that the chemical modification of GG by partial acid hydrolysis and methylation, to controlled degrees, significantly improves the interaction coefficient of GG thereby reducing the initial burst of drug release. It can be a very useful indigenous and cost effective alternative to HPMC, a widely used cellulosic hydrophilic polymer matrix for controlled release drug delivery.

5.8 REFERENCES

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