WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 9, 850-861. Research Article ISSN 2277– 7105

HPMCK4M AND GUM KARAYA: INFLUENCE ON RELEASE MECHANISM OF CARVEDILOL PHOSPHATE FROM BUCCOADHESIVE TABLETS

Gopa Roy Biswas*, **Sutapa Biswas Majee, Soumendra Mohan Saha**

Department of Pharmaceutics, NSHM Knowledge Campus, Kolkata-Group of Institutions, 124, B.L Saha Road Kolkata, Pin code-700053.

Article Received on
25 August 2014,

Revised on 18 Sept 2014,
Accepted on 13 Oct 2014

***Correspondence for Author**
Dr. Gopa Roy Biswas
Department of Pharmaceutics, NSHM Knowledge Campus, Kolkata-Group of Institutions, 124, B.L Saha Road Kolkata.

ABSTRACT

Drug release mechanism from matrix dosage form is governed by polymer swelling, polymer erosion, drug dissolution/diffusion, drug distribution inside the matrix and drug/polymer ratio. Thus for the preparation of controlled release dosage form , hydrophilic , swellable, porous polymeric material alone or in optimum combination is essential. Here a plant derived polymer like Gum karaya (GK) and HPMCK4M have been selected to prepare buccal tablets to study the buccoadhesive strength and the release kinetics of Carvedilol phosphate. Three different ratios of HPMCK4M and Gum karaya have been considered to prepare buccoadhesive tablets. Their physicochemical tests revealed satisfactory results. Buccoadhesive strength was found to be in the range of 32-36 gm, which is good enough to hold the buccal tablets inside the buccal cavity. Percent Swelling of the buccoadhesive tablets were in the range of 47.11-53.09. Swelling is maximum in the tablet where GK and HPMCK4M ratio is 1:1. Drug dissolution from buccoadhesive tablets has been described by kinetic models. The release data were fitted in different kinetic models. like zero order, first order and Higuchi . Buccoadhesive tablets incorporating HPMCK4M and GK at 5:7 and at 1:1 provided zero-order release over 8 hours. A combination of HPMCK4M with GK at 7:5 reveals the dominance of the high viscosity gel formed by HPMC and hence drug release obeyed mixed kinetics.

KEY WORDS: Gum karaya, HPMCK4M, Buccoadhesion, Release kinetics.

INTRODUCTION

Successful buccal drug delivery using buccal adhesive systems should have good bioadhesion to retain the formulation in the oral cavity and maximize the intimacy of contact with mucosa. This formulation needs a vehicle that is responsible for releasing the drug at an appropriate rate under the conditions prevailing in the mouth and successful strategies should be implemented to overcome the low permeability of the oral mucosa [1]. The use of biocompatible polymers has been the area of interest of recent research activity in the design of dosage forms for controlled release administration.

Hyroxypropyl methylcellulose (HPMC) is one of the most widely used polymers in the preparation of oral controlled drug delivery systems [2]. Hydroxypropyl methylcellulose (HPMC) products vary chemically and physically. HPMCK4M has been selected for the experiment here. To achieve controlled release through the use of a water-soluble polymer like HPMC, the polymers generally hydrate on the outer surface to form a gelatinous layer. A rapid formation of a gelatinous layer is critical to prevent wetting of the interior and also prevent rapid release of drug from the matrices [3]. Once the protective gel layer is formed, it also controls the penetration of additional water into the matrix. When the outer gel layer fully hydrates and dissolves, a new inner layer must replace it and be cohesive and continuous enough to retard the influx of water and control drug diffusion. It has been observed that the drug release profiles from matrices depend on the type and ratio of the quantity of the polymers used in combination.

One plant derived bio compatible gum has been selected for the study that is Gum karaya. Gum karaya (GK), also called sterculia gum, is the dried exudation of the Sterculia urens tree and other species of Sterculia, which belong to the family Sterculiaceae [4]. Gum Karaya is a negative colloid and a high-molecular-weight complex acidic polysaccharide. It is a partially acetylated complex polysaccharide composed of galacturonic acid, beta-D-galactose, glucuronic acid, L-rhamnose, and other residues obtained as the calcium and magnesium salt [5] .The general utility of GK is based on its viscosity. GK showed its suitability in the preparation of hydrophilic matrices [6] mini-matrices, microcapsules and transdermal patches. It has been used here in combination with HPMCK4M to prepare buccoadhesive tablets for buccal administration and to observe its influence on the release profile of drug and the buccoadhesive strength of the dosage form. A suitable buccal drug delivery system should be flexible with good bio adhesion, so that it can be retained in the oral cavity for the desired

duration releasing the drug in a predictable manner to elicit the required therapeutic response. Gum karaya, is good buccoadhesive in nature. It swells in water and has profound effect on the release kinetics of controlled release dosage form.

MATERIALS AND METHODS

Materials

Carvedilol phosphate was a gift from Macleods Pharmaceuticals Ltd, Mumbai, India. HPMCK4M (Methocel) was gifted by Colorcon, India. Gum karaya powder # 150 was obtained as gift sample from Nutriroma, Hyderabad, India. All other materials used were of analytical reagent grade.

Methods and Methodology

The drug, polymers and excipients were mixed homogeneously in a glass mortar for 15 min.The mixture was then compressed into tablets using an 8 mm, round-shaped flat punch in a single-stroke using 10 station rotary machines (Karmavati Ahmedabad, India). The tablets were prepared with different compositions and their formulations are shown in Table-1.

Table-1: Composition of conventional and buccoadhesive tablets of Carvedilol phosphate.

Ingredients	Conventional (control)	T1	T2	T3
DRUG	3%	3%	3%	3%
DCP	75%	50%	50%	50%
MCC	20%	20%	20%	20%
GK	0	12.5%	17.5%	15%
HPMCK4M	0	17.5%	12.5%	15%
TALC	2%	2%	2%	2%

* Each tablet weighs 200 mg

Drug-Excipient Interaction Study Using FTIR Spectroscopy

Drug-excipient interaction, one of the most essential parameters, is studied before development of the formulations. Carvedilol phosphate; polymers and polymer mix with drug was mixed separately with IR grade KBr in the ratio 1:100 and corresponding pellets were prepared by applying 5.5 metric ton of pressure in a hydraulic press. Polymers were HPMCK4M and gum karaya. The pellets were scanned over a wave number range of 4000 to 400 cm^{-1} in FTIR spectroscope (ALPHA T, Bruker, USA).

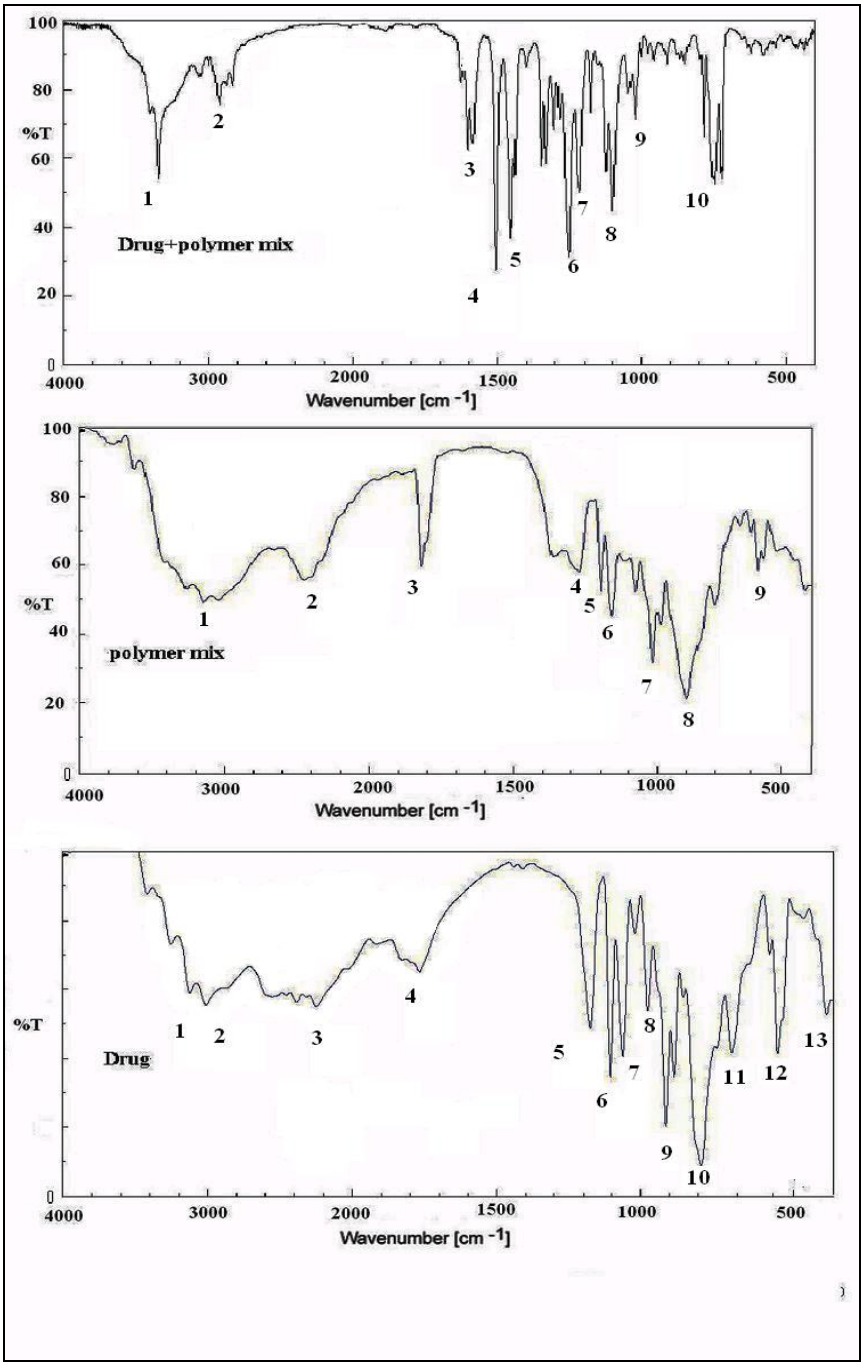

Figure 1. FT-IR spectra of A. drug, B. polymer mix and C. drug-polymer mix Differential Scanning Calorimetry (DSC)

The DSC analysis of pure drugs, physical mixture of two polymers, and physical mixture of the two polymers along with the drug was carried out separately using Pyris Diamond TG/DTA Thermo gravimetric /Differential Thermal Analyzer (Perkin Elmer Inc, PerkinElmer SINGAPORE) to study any possible drug-polymer interaction at the molecular level. The ratio of drug to polymer chosen was same as that in the final formulation. Platinum crucible was used with alpha alumina powder as reference. About 6 to 10mg sample were

kept in platinum pans at a rate of 12°C/min from 10°C to 300°C temperature range under a nitrogen flow of 150 ml/min. The changes in the DSC curves were evaluated both with the positions of peak maxima and minima. The peak areas represent the phase-transition enthalpies.

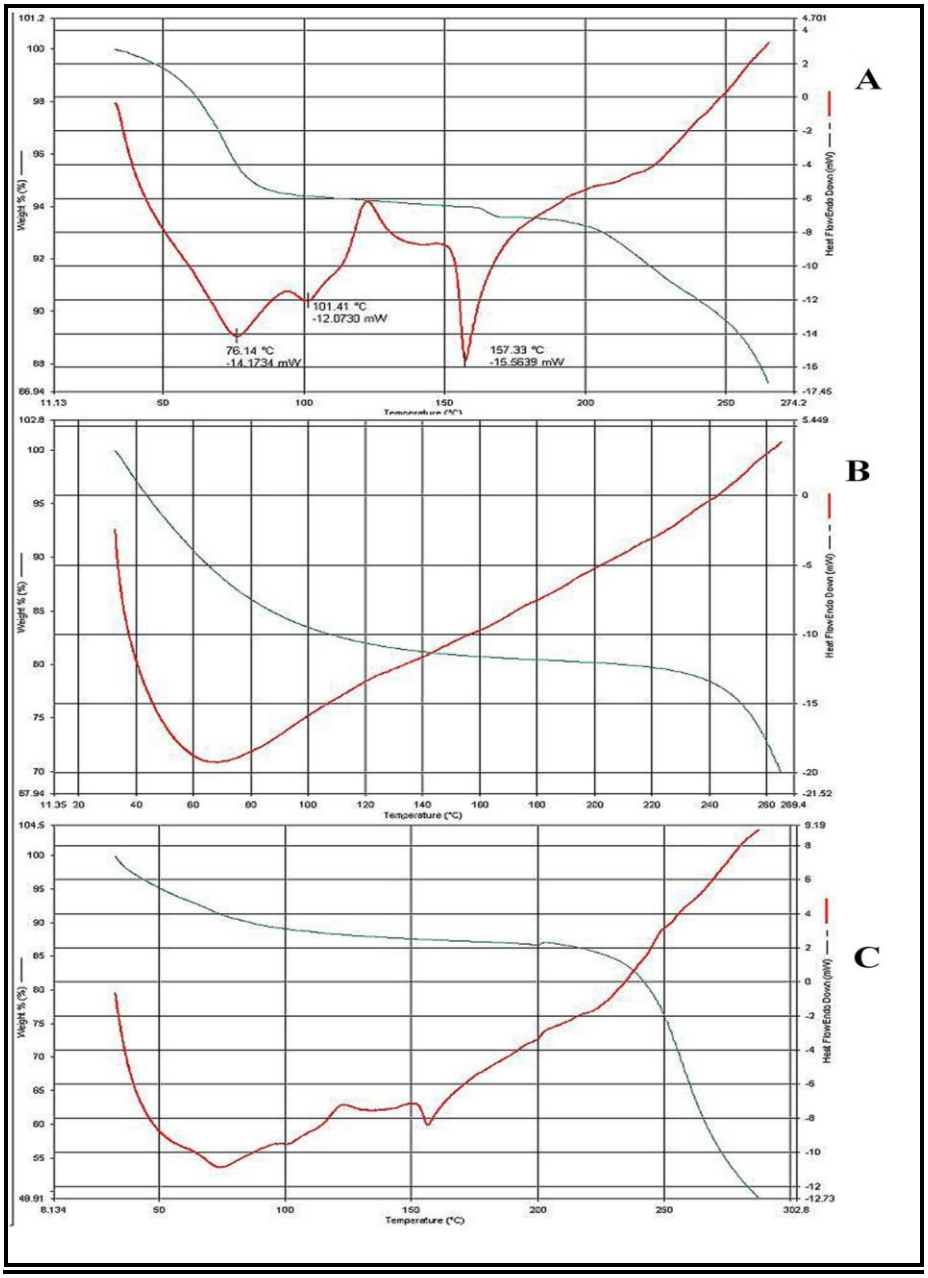

Figure-2: DSC thermogram of of A. drug, B. polymer mix and C. drug-polymer mix

Buccoadhesion Test

To determine the buccoadhesive strength of the experimental tablets, each formulation to be tested was attached to goat-buccal mucosa. A small physical balance having two circular pans (diameter, 2 cm) hanged from a rod which was balanced with a fulcrum on a stand, was used as a modified buccoadhesion test assembly [7]. Lower end of a circular pan was attached to

the buccoadhesive tablets. Immediately after the attachment weights were placed on the other pan. Placing of weights was continued till the pan got detached.

Swelling Index

the buccoadhesive tablets were weighed (W1) and placed separately in petri dishes containing 25 ml of Phosphate buffer (pH-6.8). The dishes were stored at room temperature. After 420 mins the buccoadhesive tablets were removed and the excess water on their surface was carefully removed using filter paper. The swollen tablets were weighed (W2) and the percentage of swelling was calculated by the following formula [8].

Swelling index = (W2 - W1)/W1*100

Moisture Content Capacity

To determine the moisture content capacity of the buccoadhesive tablets they were kept in desiccators for 24 hours with Silica beads. The percentage moisture content was calculated from the weight differences relative to the final weight after exposing prepared buccoadhesive tablets to activated silica in vacuum desiccators.

Table-2: Physical properties of Buccoadhesive Tablets.

Batch * N=6 Mean ± S.D	Hardness (Kg/cm^3)	Weight (mg)	Content uniformity (%)	Surface PH	Friability (%)	Buccoadhesive strength(gm)
Conventional (control)	2.3 ±0.2	185.7± 1.5	98.23 ±0.03	6.6 ± 0.1	1.4 ±0.3	-
T1	2.20 ± 0.1	186.0 ± 2.2	98.08 ± 0.03	6.75 ± 0.1	0.98 ± 0.2	32.16 ± 2.2
T2	3.50 ± 0.2	185.9 ± 3.1	98.96 ± 0.02	6.55 ± 0.2	0.86 ± 0.1	34.25 ± 1.5
T3	3.20 ± 0.2	186.0 ± 2.5	98.25 ± 0.03	6.72 ± 0.1	0.80 ± 0.3	36.32 ± 1.8

In Vitro Drug Release (Dissolution Study)

The United States Pharmacopeia (USP) XXIII rotating paddle method used to study the drug release from the buccoadhesive tablet. The dissolution medium consisted 900 ml of phosphate buffer pH 6.8. The release was performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. In this study sinker was used to prevent the float of the tablet and retain at the bottom of the dissolution vessel. Samples (5 mL) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through Whatman filter paper and analyzed after appropriate dilution (1ml of Sample in 10 ml) by UV spectrophotometer (UV – 1800 Shimadzu) at 241 nm.

Kinetics of Drug Release

To investigate the drug release kinetics from buccoadhesive tablets of Carvedilol phosphate the release rate obtained from dissolution studies were fitted to various kinetic equations [9] .The kinetics models used were a, Zero order equation($Q_t = Q_0 - K_0t$), First order equation ($Qt = \ln Q_0 - K_0t$) and Higuchi's equation($Qt = K_ht^{1/2}$).

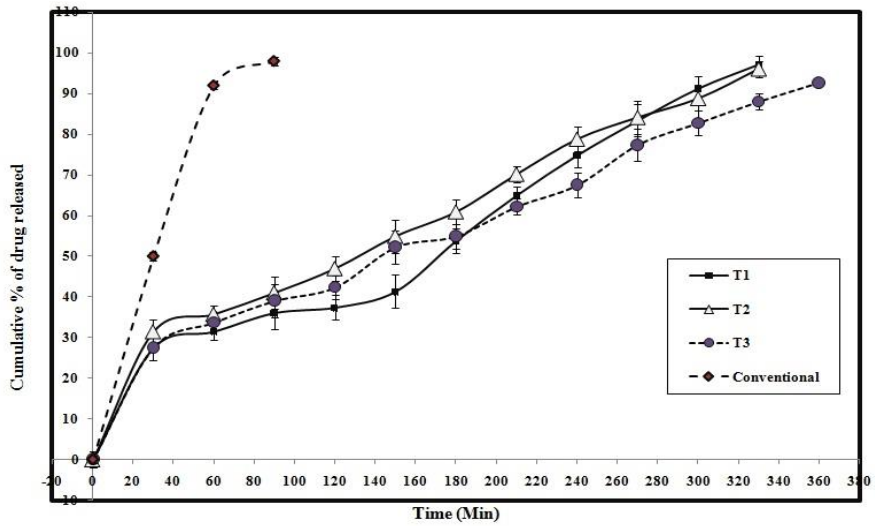

Figure-3: Drug release profile of Carvedilol phosphate from Buccoadhesive tablets in comparison with conventional (control) tablet (± SD, N=6).

Statistics

Data were assessed by one-way ANOVA followed by Tukey HSD Test using Vassar Stats software (USA). $P<0.01$ has been considered as statistical significance.

RESULTS AND DISCUSSIONS

Drug-excipient interaction is a very important pre-formulation study to develop a new formulation. Among the various methodologies available to understand the drug excipient interaction, common approaches are FTIR spectroscopy, DSC, IR-spectra etc. Here FTIR-spectroscopy shows the interaction between the molecules at the level of functional groups. IR spectra of Carvedilol phosphate and its formulations were obtained by KBr pellet method using ALPHA T, BRUKER spectrometer in order to rule out drug-carrier interaction occurring during the formulation process. Figure 1 Shows the IR spectra of a mixture of Drug, mixture of polymers (HPMCK4M+Gum karaya) and drug-polymers mix. In IR-spectra of drug-polymers mix, between 3300 cm^{-1} and 1600 cm^{-1} and between 1500 cm^{-1} and 900 cm^{1} wave numbers, variations at transmission spectroscopy data were noted. Alkanyl (-CH-)

(2950 cm^{-1}- 2800 cm^{-1}), alkenyl C=C (3100-3010 cm^{-1}) ,acetylenic (-3300 cm^{-1}), aldehyde (2850-2750 cm^{-1}) , carboxyl (3400-2400 cm^{-1}) amide (-NH) (1000 cm^{-1}- 1250 cm^{-1}) ketonyl (-C=O) (1710 cm^{-1}-1720 cm^{-1}), phenolic (-OH) (970 cm^{-1}-1250 cm^{-1}) stretches are mainly responsible for those regions. This suggests that there may be physical interactions related to the formation of weak to medium intensity bonding since no major shifting of peaks was noted [10].

DSC measurement was carried out to provide better evidences whether predicted physical interaction would lead to drug amorphous formation in the formulations. Figure 2A shows the DSC and TGA of Carvedilol phosphate. Figure-2B. Shows the DSC and TGA of polymeric mixture (HPMCK4M and Gum karaya) and Figure 2C represents DSC and TGA of those above mentioned polymeric mixture along with Carvedilol phosphate.

Figure 2C shows dipping of curve at 78.27^{o}C claiming the loss of water molecule from Carvedilol phosphate .This was followed by the crystallization of Carvedilol phosphate molecules at 157.11^{o}C. When the drug molecules reached at 157.11^{o}C they gained enough energy to move into very ordered arrangement for crystallization. The changes in all the DSC thermograms correspond to the changes at the respective TGA shown in the Figure 2 depict the DSC and TGA of the polymeric mixture. Figure 2C is the thermo gram for the mixture of drug and the polymers in which the peak at 157.27^{o}C is intact but the peak is quite shortened. This suggests solid solution interactions between the drug and the polymers. The buccal tablets show satisfactory physical-mechanical properties. In the entire four formulations drug content is above 98% and the low values of standard deviation and coefficient of variation (<1) indicate uniform distribution of the drug within the buccoadhesive tablets. The surface pH obtained (Table 2) in this study were within the limits and showed hardly any variation from time to time which omits the chances of irritation in the buccal mucosa upon application. All the three types of buccal tablets exhibited good Buccoadhesive strength; those were found to be 32.16, 34.25 and 36.32 g respectively. In case of the mucoadhesive polymers desired strength was reported to be about 30 g [11]. Hence the buccoadhesive strengths were found to be satisfactory to hold the buccal tablet inside the oral cavity. That strength of tablet was found to be a function of the nature of polymers used and their ratio in combination.

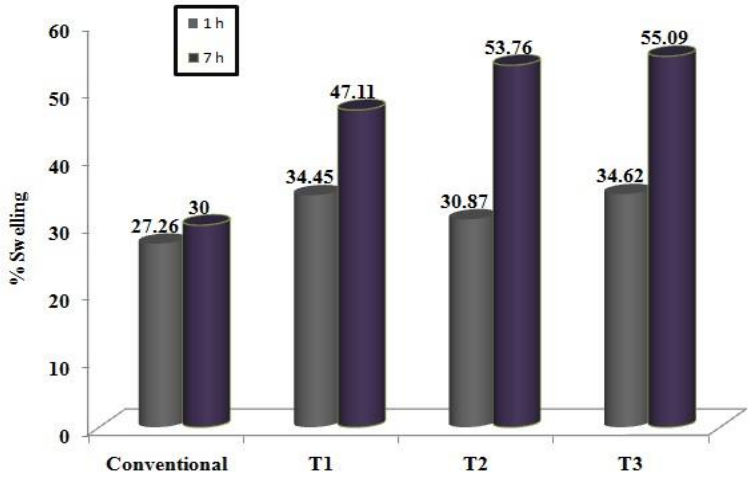

Figure-4: Percent swelling of the buccoadhesive tablets

For T2 the swelling was 51.43 % and for T1 and T3 they were 47.11 % and 53.09 % respectively. The highest hydration (swelling) was observed with the formulation T3. Buccoadhesion occurs shortly after swelling but the bond formed between mucosal layer and polymer is not very strong at the beginning. The adhesion will increase with the degree of hydration to an optimum value. Results indicate that swelling is maximum in T3 where HPMCK4M : GK is 1:1.Buccoadhesive strength is also maximum in T3 and that supports the above findings.The result of moisture content for T1, T2 and T3 were 14.87%, 16.71% and 50% Fig 3 represents the graph consisting of cumulative percentage of drug release vs time. Drug release is the slowest one in T3, where HPMCK4M and GK are present at 1:1 ratio. In formulation T1, t_{50}% value is 2 hr 30 minutes whereas in T2 and T3 they are 35 and 32 minutes respectively. From all the formulations 90 % of the drug got released over 7 hours. The release data were fitted in different kinetic models (Table 3). Buccoadhesive tablets T2 and T3 followed zero order kinetics (r^2 = 0.9954 and 0.9952 respectively). This forms released the same amount of drug by unit of time.T1 releases drug via mixed kinetics. In first 3 hours drug release from T1 followed zero order kinetics (r^2= 0.9951) followed by first order kinetics (r^2=0.9852) from 3 hours to 8 hours. In T1 in the first few hours the soluble drug comes out and porous matrices are formed .Release of drug from that porous matrices will be directly proportional to the amount of drug present in the interior [12]. Gum karaya and HPMC-containing tablets take up water on contact with the dissolution medium thus allowing dissolution of a certain percent of the drug found at and near the tablet surface prior to gel or viscous medium formation [13].

The release of drug from a gelatinous swollen mass, which controls the diffusion of drug molecules through the polymeric material into aqueous medium, was steadier in T2 than the T1 and T3. In T2 due to higher percentage of gum karaya provides a much more controlled release of the drug due to its very slow erosion rate [14] and moderate swellability. Generally the viscosity of the gel layer around the drug particles in the tablet increases with increase in hydrogel concentration thus limiting the release of the drug [15].

CONCLUSION

It can be concluded that Gum karaya and HPMCK4M in different ratio can be used for the formulation of buccoadhesive tablets of Carvedilol phosphate. This type of tablets shows good buccoadhesion property. Drug release kinetics from the buccal tablets containing different polymeric combinations has been observed. In the buccoadhesive tablet where GK: HPMCK4M is 1:1 and where GK: HPMCK4M is 7:5; drug release obeyed zero order kinetics through out the study. So it can be further concluded that the formulation where percentage of GK is more than HPMCK4M, drug release is much more controlled among all.

Table 3: Release rate constants for the drug Carvedilol phosphate from the Buccal tablets obtained from different kinetic models.

Batch	K_1	R_1^2	K_2	R_2^2	K_3	R_3^2
Zero order						
Conventional	0.2763	0.8454	-	-	-	-
T1	0.2498	0.9733	-	-	-	-
T2	0.2226	0.9954	-	-	-	-
T3	0.2027	0.9952	-	-	-	-
Higuchi						
Conventional	-	-	6.8579	0.9467	-	-
T1	-	-	6.2148	0.9298	-	-
T2	-	-	5.6435	0.9705	-	-
T3	-	-	5.332	0.9585	-	-
First order						
Conventional	-	-	-	-	0.029	0.9995
T1	-	-	-	-	0.0041	0.8055
T2	-	-	-	-	0.0036	0.872
T3	-	-	-	-	0.0025	0.9243

ACKNOWLEDGEMENT

The authors are thankful to NSHM Knowledge campus, Kolkata for providing necessary facilities to carry out the research work and Metallurgy Department, Jadavpur University to provide DSC facility.

REFERENCES

1. Devai KGH, Kumar TMP, Design and in-vitro evaluation ofmucoadhesive buccal tablets of repaglinide. Ind. J Pharm Sci, 2004; 4(1):438-444.
2. Gafourian T, Khosro A, Parviz F, Safari A, Nokhodchi A.Drug Release Study from Hydroxy propyl methylcellulose (HPMC) Matrices Using QSPR Modeling. J. Pharm. Sci. 2007; 96: 3334-3351.
3. Choi HG, Jung JH, Yong CS, , Rhee CD, Lee MK, Han JH, Park KM, Kim CK. Formulation and in vivo evaluation of omeprazole buccal adhesive tablet. J. Contr. Rel. 2000; 68: 405-412.
4. Whistler RL, Bemiller JN. In Industrial gums: polysaccharides and their derivatives. Academic Press, San Diego, 1993; 318–337.
5. Weiping W. Tragacanth and karaya, in: Philips GO, Williams PA (Eds.). Handbook of Hydrocolloids. Woodhead, Cambridge.2000; 155.
6. Murali Mohan Babu GV, Himasankar K, Narayan CPS, Ramana Murthy KV. Controlled release of diclofenac sodium by gum karaya-chitosan complex coacervate: in vivo evaluation. Ind. J. Pharm. Sci. 2001; 63:408–412.
7. Gupta A, Garg S, Khar RK. Measurement of bioadhesive buccal tablets: design of an in vitro assembly. Indian Drugs, 1993; 30: 152-160.
8. Vishnu MP, Bhupendra GP, Harsha VP. Karshanbhi MP. Mucoadhesive bilayer tablets of propranolol hydrochloride. AAPS Pharm. Sci. Tech. 2007; 8(3): Article 77.
9. Mathew ST, Devi SG, Sandhya KV. Formulation and evaluation of ketorolac tromethamine- loaded albumin microspheres for potential intramuscular administration. AAPS Pharm SciTech, 2007; 8(1): E1-E9.
10. Mukherjee B, Das S, Patra B, Layek B. Nefopam containing transdermal- matrix based on pressure-sensitive adhesive polymers. Pharm. Tech. 2006*; 30*:146-18.
11. Singh B, Ahuja N, Development of controlled-release buccoadhesive hydrophilic matrices of diltiazem hydrochloride: optimization of bioadhesion, dissolution, and diffusion parameters. Drug Dev .Ind. Pharm, *2002;* 28: 431-442.
12. Mulye NV, Turco SJ. A simple model based on first order kinetics to explain release of highly water soluble drugs from porous dicalcium phosphate dihydrate matrices. Drug Dev. Ind. Pharm, 1995; 21: 943–953.
13. Kotadiya R, Patel V, Patel H. Comparative evaluation study of matrix properties of natural gums and semi-synthetic polymer. J Pharm Res, 2008; 1: 208–14.

14. Sujja-areevatha J, Mundaya DL, Cox PJ, Khan KA. Relationship between swelling, erosion and drug release in hydrophillic natural gum mini-matrix formulations. Eur.J Pharm. Sci, 1998; 6: 207–218.
15. Chandran S, Ravi R, Saha RN. Development and In vitro Evaluation of Oral Controlled Release Formulations of Celecoxib Using Optimization Techniques. Yakugaku Zasshi, 2006; 126(7): 505-11.