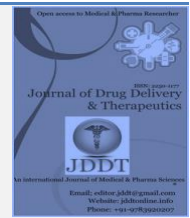


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Research Article

## Evaluation of Drug Release from Carboxymethyl Starch-Xanthan Gum-HPMC Matrix

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### Abstract

The use of hydrophilic polymers from natural origin. Especially the polysaccharides have been the focus of current research activity in the design of matrix device due to their non toxic, biocompatible, biodegradable nature and broad regulatory acceptance. A large number of polysaccharides such as Carboxymethyl starch, Xanthan gum, Hydroxy propyl methyl cellulose (HPMC), Sodium Alginate etc, have been used as hydrophilic matrices to investigate release behavior of drug. In order to enrich the resources, there is a quest for new polysaccharide owing to their diverse chemical composition and functional groups are amenable to chemical modification and thus tailor made polymeric matrices are obtained which which can be used to modulate oral drug release. The objective of the study is to characterize Verapamil hydrochloride loaded matrix dosage form using hydroxy propyl methyl cellulose (HPMC), xanthan gum, corn starch as rate retarding polymer. Dosage forms were prepared using different polymers along with drug Verapamil hydrochloride. Carboxymethylation was performed. Drug release was evaluated in simulated gastric media. Addition of xanthan gum significantly retarded the burse release of drug. The retardation of drug release was found to be dependent upon the concentration. The formulation composed of HPMC K4M and CS (ARI-ARI3) followed super case transport is swelling controlled, purely relaxation controlled drug delivery.

**Keywords:** Verapamil HCl, Natural gums, xanthan gum, HPMC, sustained release

## INTRODUCTION:

The oral route is the most common route for drugs that have a "small absorption window in the gastrointestinal tract (GIT)". For drugs with an absorption window in the GIT, it is essential that drugs are not delivered significantly beyond the desired site of action or absorption. Regulated release systems are also developed to accomplish this purpose. These drug delivery systems monitor not only the rate at which the drug is released over time (temporary control), but also the place from which the drug is distributed (spatial control) <sup>1</sup>.

Many of these managed delivery systems use hydrophilic polymer matrices that provide the delivery of sparingly soluble drugs with useful levels of control. These matrices do not provide adequate control over the rate of drug release for soluble drugs, especially for highly soluble drugs, but instead result in a release that approximates first-order kinetics. That is, the release rate is an inverse function of the elapsed time's square root. With this release pattern, in the acidic atmosphere of the belly, much of the medication in the matrix is always released within the first hour <sup>2</sup>. The retention of the drug delivery system in the belly & the rate at which the drug is released is very critical for drugs such as Verapamil Hydrochloride (VHCL), whose solubility and hence absorption decreases with an increase in pH. An approach to prolonging VHCL retention in the stomach and

controlling its rate of release from the dosage type is to grow a polymer matrix capable of swelling and erosion in the acidic stomach environment to form a hydrodynamically balanced mass swelled but erodible <sup>3</sup>. It is expected that the swelling of the polymer matrix will result in low density mass from such an in situ forming hydrogel and continuous erosion will cause a constant delivery rate of the drug from the matrix <sup>4</sup>.

In the current investigation, for the engineering of the polymer matrix, pH independent swellable and erodible HPMC K4M and pH based swellable carboxymethylated Locust bean gum (CLBG) or Tamarind Seed gum (CTSG) were used. LBG is a galactomannan of high molecular weight that has a straight chain of mannose units connected to this linear chain of galactopyranose units. It is a neutral, non-gelling polysaccharide that requires high temperatures and intense agitation to dissolve fully in water. It is needed to heat LBG to about 60-85 °C for full hydration in an aqueous medium. A disordered, fluctuating, random coil conformation is adopted by dissolved LBG <sup>5, 6</sup>. Pseudoplasticity is present in the LBG solution (shear-thinning behaviour), which at enhanced shear rate shows reduced viscosity and "can form a weak gel network with concentrations as low as 0.5%" <sup>7</sup>. The FDA classifies it as GRAS and uses it for its properties of stabilising, thickening, and fat-replacing.

Verapamil HCl is the “first CCB to be discovered was verapamil, a part of the phenylalkylamine (PAA) subclass of CCB, and it was the only member of this subclass to be commonly used for hypertension, in domain III and IV of the alpha1 subunit of the VGCC, Verapamil binds to amino acids in the S6 segments”. The PAA compulsory position overlaps with the site where DHP and verapamil binding can result in DHP binding allosteric modulation <sup>8</sup>.

## MATERIALS AND METHODS

**Materials:** Verapamil HCl was obtained as gift from Sun Pharmaceuticals India Xanthan gum (XG) & HPMC K4M were procured from Sigma Aldrich. All other substances were of analytical grade All chemicals were pure and from analytical grade.

### Methods:

**Fourier Transform Infra-Red spectroscopy (FTIR):** For qualitative compound recognition, FTIR analysis of the samples was carried out. The pellet KBr from appx. It was prepared to grind 2 mg of the tester with 200 mg of KBr in a pressure compression system 1 mm diameter of the products. The sample pellet was placed and scanned in the FTIR compartment at a wavelength of  $4000\text{ cm}^{-1}$ - $400\text{ cm}^{-1}$ . <sup>9</sup>

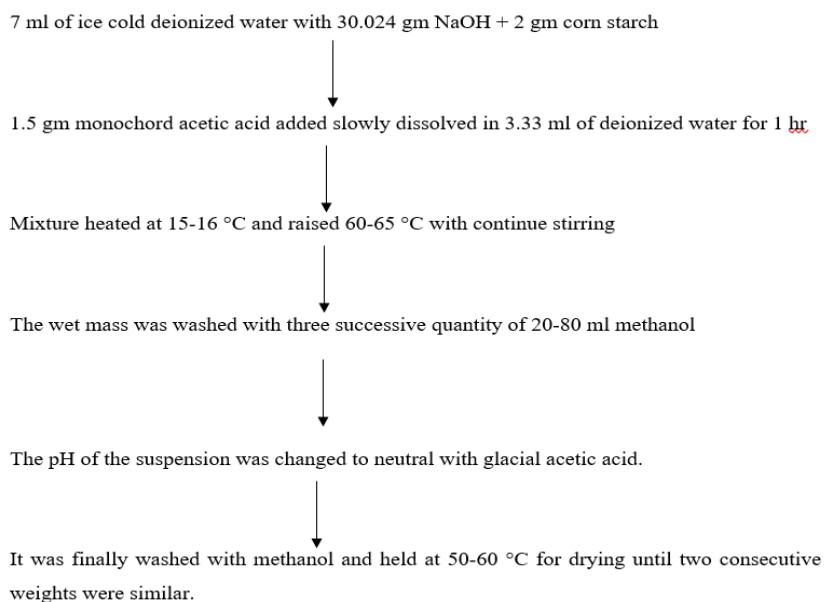
**Ultraviolet Absorption (UV):** UV spectrum in the range 200-400 nm of 100 µg/ml 0.1M HCl solution was determined.

**Differential Scanning Calorimetry (DSC):** For the detection of verapamil HCl used in the current investigation, DSC was used. The DSC analysis was carried out at an interval of 5 ° C/min at 50-250 ° C. In crimped aluminium pans, duplicate samples of 5 mg are used. Indium samples were used for calibrating the DSC tools. <sup>10</sup>

**Quantitative estimation of drug by ultraviolet spectrometer:** The estimation of the drug, the UV spectrophotometric method was selected because the method is simple, economical and gave reproducible results within the appropriate limits. The UV spectrophotometer double beam (UV-1800, Shimadzu) was used for the study.

**Determination of Absorption Maxima:** A 1% w/v solution of verapamil HCl 0.1M HCl, between 200-400 nm ( $\lambda_{\text{max}}$ ) was scanned to determine the UV absorption limit.

### Preparation of carboxymethyl starch



**Preparation of 0.1M HCl solution:** Around 8.5 HCL was dissolved in ample filtered water to produce 1000 ml of HCL.

**Preparation of standard calibration curve:** Verapamil HCL (2-10 µm concentration range) demonstrated peak absorbance at 0.1M HCl at 278 nm. Shimadzu (UV-1800) UV-visible spectrophotometer are used.

### Procedure:

**For Standard solution:** 100 ml volumetric flasks were taken correctly weighed 100 mg of verapamil HCl and dissolved in a small amount of 0.1 M HCl, the volume was composed of a buffer, to obtain a solution comprising 1 mg/ml.

**For Stock Solution:** A stock solution was prepared from the standard solution by pipetting one ml of the above std. solution into another 100 ml conical flask and the vol. was created with the buffer to provide a solution containing 100 µg/ml.

**For Preparation of working standard solution:** In 10 ml volumetric flasks, “aliquots of 2, 4, 6, 8, and 10 ml of stock solution” were pipetted out. The volume was generated with a buffer up to the level. These dilutions give a “verapamil HCl concentration of 2, 4, 6, 8, and 10 µg/ml”. Using the Shimadzu UV-1800 spectrophotometer, the absorption of prepared solutions was measured at 250 nm against a suitable 0.1 M HCl blank. The absorption data for the standard verapamil HCl calibration curve are given in, respectively. The normal calibration curve yields a straight line, which indicates that in the concentration range 2-10 µg/ml the drug complies with Beer's rule <sup>11,12</sup>.

**Drug Polymer Interaction Study:** It is important to take into account the compatibility of drugs and polymers used within the system when developing any drug delivery system. It is also important to ensure that, under laboratory conditions and shelf-life, the drug does not interfere with the polymer. It is possible to do interaction studies on the basis of UV and DSC. The medication polymer collaboration experiments were performed for the current study by contrasting it with DSC's pure drug and drug polymer formulations <sup>13</sup>.

**Determination of degree of substitution (DS):** In 5 ml of 80% methanol, 500 mg of carboxymethyl starch was correctly weighed and dispersed; concentrated HCl was applied at slight excess and stirred for 2-3 hours. "By Whatmann filter paper no., the mixture was filtered and the residue was washed with 5 ml methanol successively until the washings showed neutrality. The residue has been dried to a steady weight. 200 mg of the dried sample was correctly

measured in an Erlenmeyer flask. 1.5 ml of 70% methanol was added and permitted to stand for a few minutes after adding 20 ml of water and 5 ml of 0.5N NaOH. The combination was shaken for 3-4 hours until the tester was fully dissolved and the solution was then titrated back to a phenolphthalein end point with 0.4N NaOH<sup>14</sup>. The DS of the O-carboxymethyl group was determined using the following formula:

$$DS = 0.162A / 1 - 0.058A$$

Where A is the milliequivalent of NaOH required per gram of sample.

#### Preparation of capsule formulations:

Single unit capsule set by bodily mixing VHCL with the necessary amount of polymers, as shown in **Table 1**, for 15

minutes using a double cone blender, followed by encapsulation into hard gelatin capsules.

**Table 1: Composition of formulations containing Verapamil HCl**

Formulation code	HPMC K4M (mg)	CS (mg)	Xanthan gum(mg)	VHCL (mg)
AR1	200	10	-	100
AR2	200	10	-	100
AR3	200	10	-	100
AR4	200	10	30	100
AR5	200	10	30	100
AR6	200	10	30	100

#### In-vitro drug release study:

Verapamil HCl in vitro drug release from capsules was assessed with a type II USP XXXI dissolution apparatus (paddle type, Electro lab, Mumbai, India) at 50 rpm at 900

ml 0.1M HCl at 37±0.5 °C. A 1 ml aliquot was removed at fixed intervals and replenished with an equal quantity of fresh dissolution medium (Table 2). UV spectrophotometric analysis of the withdrawn samples was conducted at 278 nm.<sup>15,16</sup>

**Table 2: Dissolution profile for in-vitro drug release study**

Apparatus	Parameters
Dissolution apparatus	USP Type 2, paddle
Dissolution media	0.1 M HCl
Rotation speed	50 rpm
Volume of media	900 ml
Lambda max	278 nm
Temperature	37 ± 0.5 °C

## RESULTS AND DISCUSSION:

**Characterization of Drugs:** The identities of drugs were made by spectral comparison using FT-IR, DSC and UV analysis.

**FTIR characterization of drug:** At wave numbers, the FTIR spectra of pure Verapamil HCl demonstrated distinctive peaks of "2990 cm<sup>-1</sup> (C-H stretching of methyl and methylene

group), 2957 cm<sup>-1</sup>, 2936 cm<sup>-1</sup> (C-H stretching), 2840 cm<sup>-1</sup> (C-H stretching of methoxy group), 2541 cm<sup>-1</sup>, 2452 cm<sup>-1</sup> (N-H stretching of N stretching of protonated amine), 2236 cm<sup>-1</sup> (C alkyl nitrile group), 1608 cm<sup>-1</sup>, 1592 cm<sup>-1</sup>, 1518 cm<sup>-1</sup> (stretching due to skeletal vibrations of the benzene ring), 1461 cm<sup>-1</sup> (C=C stretching due to aromatic ring), 1259 cm<sup>-1</sup>, 1142 cm<sup>-1</sup> (C-O stretching), 1026 cm<sup>-1</sup> (C-N stretching) and 816 cm<sup>-1</sup> (meta substituted benzene)".

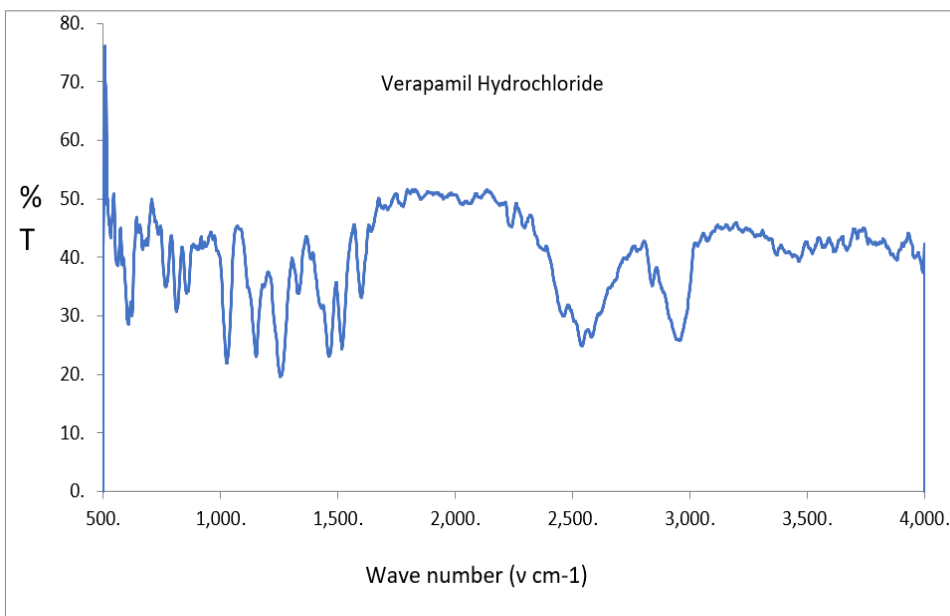


Figure 1: FTIR spectra of Verapamil HCl

**Differential Scanning Calorimetry (DSC):** Two peaks exhibit the DSC curve. The first is due to the API melting (initial temperature: ~142 °C) and the second to the decomposition.

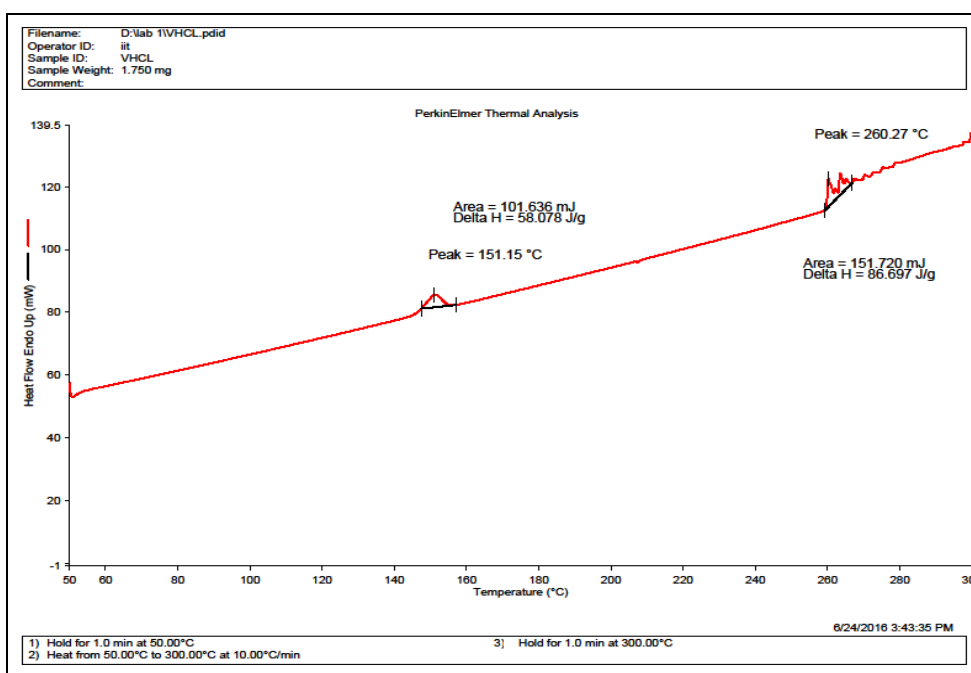


Figure 2: DSC thermogram of Verapamil HCl

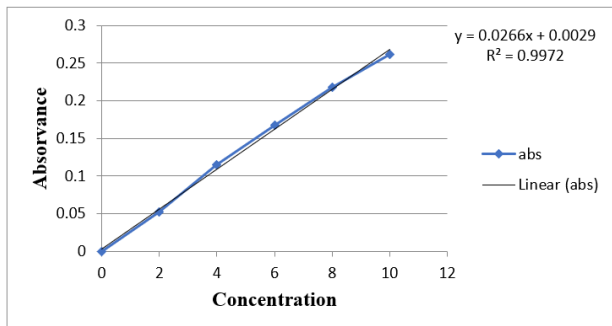
**UV Characterization of drug:** As determined by the UV-spectrophotometer, the drug absorption limit was found to be 278 nm in a 0.1M HCl solution, when scanned between 200-400 nm. The method of analysis was found to be reproducible using a verapamil HCl UV spectrophotometer at a scanned lambda max of 278 nm. The typical calibration curve of verapamil HCl at wavelength 278 nm UV-spectrophotometer was prepared at 0.1M HCl. As indicated by the statistical analysis performed, the drug absorption data in table 6.1 were found to follow Beer's Law within the specified range. The data in the **Table 3** were found to have almost perfect correlation coefficients and were found to be linear in nature. The standard curves are shown in figure 3.

Table 3: Calibration data of Verapamil HCl 0.1M

Sr.no.	Conc. (mcg)	Absorbance
1	0	0
2	2	0.052
3	4	0.115
4	6	0.168
5	8	0.218
6	10	0.262

**Table 4: Statistical parameter related to standard curve of Verapamil HCl**

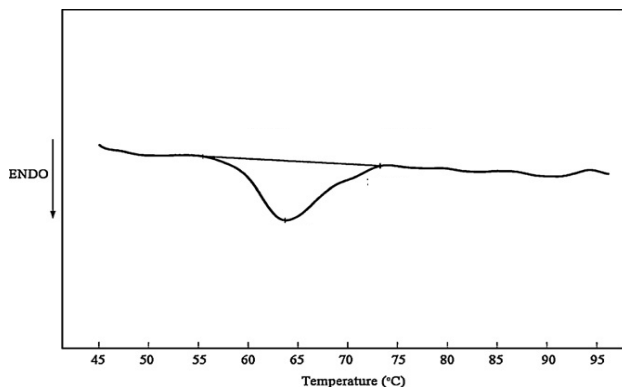
S. No.	Parameter	Values
1	Regression coefficient	0.9972
2	Equation of time	$Y=0.0266x+0.0029$



**Figure 3: Calibration curve of Verapamil HCl**

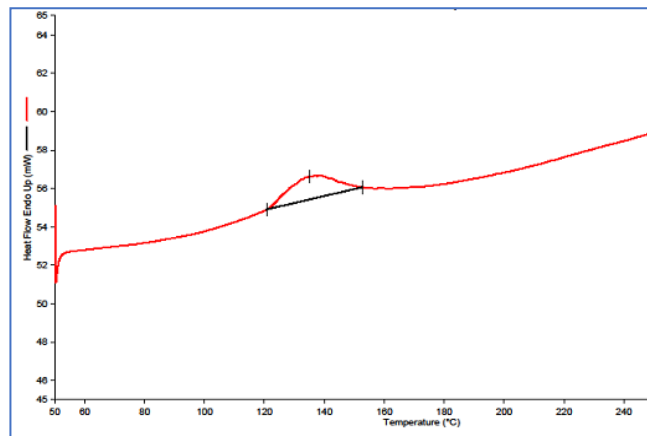
**Drug-Polymer Interaction study**

**DSC characterization of Corn Starch:** At 64 °C, the DSC corn starch thermogram displayed a large endothermic peak attributed to the glass transition temp. of corn starch.



**Figure 4: DSC thermogram of corn starch**

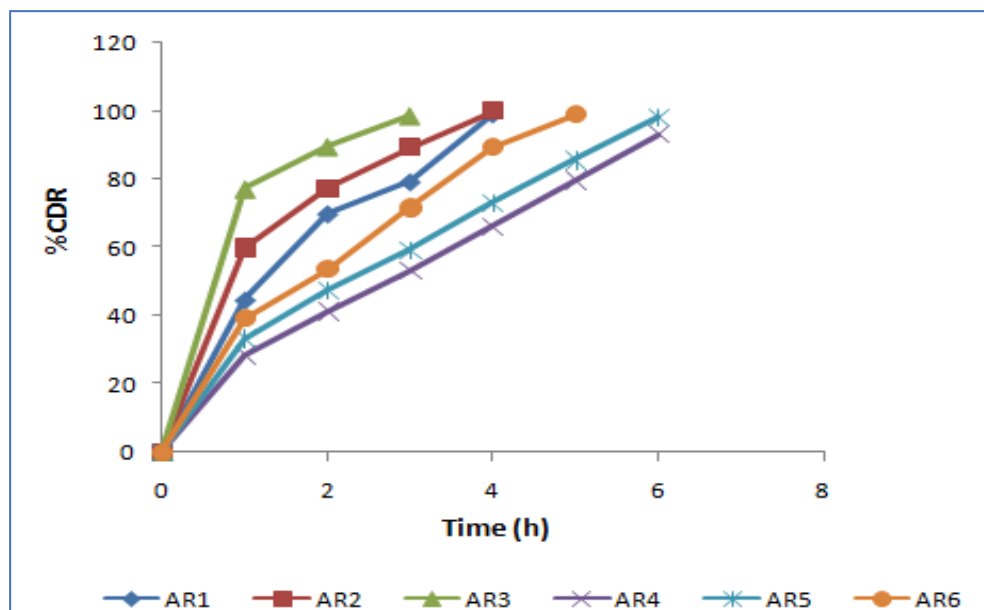
**DSC characterization of Carboxymethyl corn starch (CS):** A wide heat-absorbing crest at 130 °C accredited to the glass transition temp. of CS was shown by the DSC thermogram of CS.



**Figure 5: DSC thermogram of Carboxymethyl corn starch**

**In-vitro drug release studies:** Using the USP apparatus 2 paddle style dissolution tester containing 500 ml of 0.1 M HCl as a dissolution medium maintained at  $37 \pm 0.5$  °C with a stirring speed of 50 rpm, the in-vitro release of verapamil HCL from hydrodynamically balanced capsules was carried out for 6 hours. All the formulations stayed buoyant on the dissolution medium during the dissolution tests. The AR1-AR3 formulation remained buoyant for about 4 hours, while the AR4-AR6 formulation remained buoyant for up to 8 hours.

1 ml of solution was withdrawn and spectrophotometrically tested for the drug content at 278 nm at one-hour intervals. At the sampling point, the volume of the dissolution medium was changed to 500 ml by replacement with 1 ml of the same medium. Figure 6 include the release data from the formulations.



**Figure 6: % Drug release**

From the data it was observed that formulation composed of HPMC K4M and CS (AR1-AR3), there was burst release of Verapamil HCl. It was also observed that as the concentration of CS in the polymeric matrix was increased, drug released increased. This could be attributed to the rapid swelling of CS in the polymer matrix. Because of this rapid swelling, the polymer matrices couldn't hold their integrity and burst apart, leading to very rapid drug release. In case of formulations (AR4-AR6), xanthan gum was additionally added to the HPMC K4M+CS based polymeric matrices. It was observed that, addition of xanthan gum significantly retarded the burst release of drug. However, here also, retardation of drug release was unearthed to be dependent upon the conc. of CS in the matrix. The reason for drug retardation could be ascribed to the thick gel formation due to the existence of Xanthan gum in the polymeric matrices.

## CONCLUSION:

Dosage forms were prepared using different polymers along with drug Verapamil hydrochloride. Carboxymethylation was performed. Drug release was evaluated in simulated gastric media. Addition of xanthan gum significantly retarded the burst release of drug. The retardation of drug release was found to be dependent upon the concentration. The formulation composed of HPMC K4M and CS (ARI-ARI3) followed super case transport is swelling controlled, purely relaxation-controlled drug delivery.

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**Conflict of Interest:** Nil

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