Journal Of Harmonized Research (JOHR)

Journal Of Harmonized Research in Pharmacy
7(2), 2018, 49-56

ISSN 2321 – 0958

Original Research Article

DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE TABLETS FOR HIGHLY WATER SOLUBLE DRUG

Smita R. Narnaware, Jayshree V. Patil, Shabnam Saher, Archana Bhuyar

Department of Pharmaceutical Sciences, Nagpur University, Nagpur, Maharashtra, India- 440033

Abstract: Sustained release tablets reduce the frequency of the dosing and increase the effectiveness of the drug by localization at the site of action, providing uniform drug delivery. Verapamil hydrochloride was considered as an ideal drug for designing sustained release formulation because of the high frequency of administration and short biological half-life. Therefore, in the present study, sustained release tablets of verapamil hydrochloride were prepared by using synthetic hydrocolloids like HPMC K4M, K15M, and K100M and using interaction of natural gums like carrrageenan and chitosan. Before using carrrageenan and chitosan an attempt was made to study the mechanism of interaction of carrageenan and chitosan by FT-IR spectroscopy, x-ray diffraction spectroscopy and differential scanning calorimetry. Then these prepared tablets were evaluated for various parameters such as hardness, friability, thickness, weight variation and the formulations were found to be within limits. The *in vitro* drug release profile of the various formulations was performed. In pH 1.2 buffer Peppas model was found to be the best fit model of drug release and a better control on drug release can be obtained by varying the proportion of HPMC K4M, K15M and K100M. Hence, it was concluded that the drug release can be effectively controlled for a highly water soluble drug verapamil HCI using synthetic hydrocolloids and interaction of natural gums carrageenan and chitosan.

Keywords: Sustained release tablet, Verapamil hydrochloride, Hydrocolloids, Carrrageenan, Chitosan

Introduction: A sustained-release dosage form is defined as "any drug or dosage form modification that prolongs the therapeutic activity of the drug" [1]. The goal of sustained release dosage form is to maintain therapeutic blood or tissue level of drug for extended period of time. This is generally accomplished by attempting to obtain zero-order release from dosage form, but actually sustained release usually try to mimic zero- order release by providing drug in slow first order. Sustained release dosage form is most applicable for drugs having low therapeutic indices and short

For Correspondence:
smitanarnaware786@gmail.com.
Received on: February 2018
Accepted after revision: March 2018

elimination half life [2]. Development of oral sustained release (SR) tablets of highly water soluble drugs or bioactives has always been a challenge and therefore, opportunity for formulation scientist. Most of these drugs if not formulated properly, may be released at a faster rate resulting in exceeding the maximum therapeutic levels and hence will lead to toxic side effects. Sustained delivery of such drugs ensures improved drug delivery and patient compliance, greater safety and efficacy, desired release kinetics and helps in maintaining the plasma drug concentration within the therapeutic window for extended period of time [3,4].

There are various types of sustained release forms [5], but a hydrocolloid system includes unique, hydrodynamically balanced drug delivery system (HBS). There are various instrumental methods such as FT-IR spectroscopy; X-ray diffraction spectroscopy and Differential scanning calorimetry are used to study the interaction of hydrocolloids [6].

Verapamil hydrochloride is a phenyl alkylamine calcium channel blocker and class IV antiarrhythmic that is widely used in the management of hypertension, ischemic heart disease such as angina pectoris, mycocardial infarction and arrhythmias [7]. Its serum concentration differs from 20 to 500 ng/ml depending on the administered dosage form and there is considerable interindividual variation, which might be, in part; due to variation in the extent of hepatic metabolism [8-10]. The oral absorption of the drug from oral dosage forms is about 90% but it is subjected to a very extensive first-pass metabolism in the liver [11] and its bioavailability is only about 20% [8, 12, 13]. Since this drug has a short elimination half-life of 2 - 4 hours and is eliminated rapidly, repeated daily administrations are required to maintain effective plasma levels [14]. It has been suggested that drugs with biological half lives in the range of 2-8 hours are good candidates for sustainedrelease formulations [15].

Hence the objective of present study was to develop a sustained release tablet of verapamil hydrochloride by using synthetic hydrocolloids like HPMC K4M, K15M, and K100M and using interaction of natural gums like carrrageenan and chitosan for better control of drug release.

Experimental

Materials: Verapamil Hydrochloride was a gift from Nicolas piramal India Ltd, Mumbai, India. Carrageenan, Chitosan and Microcystalline cellulose were obtained from Signet chemical corporation Pvt. Ltd, Mumbai, India. Magnesium stearate and Isopropyl alcohol was purchased from Samar chemicals, Nagpur, India. Potassium dihydrogen orthophosphate was obtained from Loba chemie Pvt. Ltd. Mumbai, India. Sodium hydroxide and Concentrated HCI were purchased from SD Fine chemicals, Mumbai, India. HPMC K4, K15, K100 was obtained from Colorcon Ltd., Goa, PVP K30 from Zim labs, Nagpur and Acetic acid from Merck Ltd., Mumbai, India.

Calibration curve of Verapamil hydrochloride in pH 1.2 buffers as well as in 6.8 pH buffer:

- **Standard Stock Solution:** Separately, weighed 100 mg of Verapamil hydrochloride and transferred to two separate 100 ml volumetric flask. In one flask pH 1.2 buffers was added to dissolve drug and volume was made up to 100 ml while in another flask pH 6.8 phosphate buffer was added, shake well and make up the volume to 100 ml. From both the solutions, 10 ml in each was transferred to 100 ml volumetric flask separately and volume was made up to 100 ml with respective buffers.
- **Working Stock Solution:** A series of Verapamil HCI solutions ranging from 10 to 100jag/ml were prepared from both the standard stock solution. The absorbance of the solutions was measured spectrophotometrically at 278 nm.

Development of Verapamil HCI sustained release tablets: For the development of sustained release tablets, HPMC K4M, K15M, and K100M were used individually in various proportions 40, 60, 80 and 100% proportion as compared to drug amount as a sustained release polymer. The Verapamil HCI, microcrystalline cellulose PH 101, and polymer were sifted through 40 # sieve. The binder solution was prepared by dissolving PVP K-30 in isopropyl alcohol. The blend was granulated using blinder solution and dried at 45-55°C for 24 hours. The granules were sifted through 16# sieve. The fines were separated and to it, talc and magnesium stearate were added. The tablets were compressed using 8 mm standard biconcave punches at a weight of 250 mg. The compression pressure was adjusted between 2.5 to 3 kg/cm2. The formulation of the sustained release tablets using HPMC K4M, K15M and K100M was shown in table 1.

Table 1: Formulation batches containing HPMC K4M, K15M and K100M

Batch Containing HPMCK4M				
Ingredients	**40%**	**60%**	**80%**	**100%**
Verapamil HCI	120	120	120	120
HPMCK4M	48	72	96	120
MCCPH101	64.5	40.5	16.5	-
PVP K30	12.5	12.5	12.5	12.5
Talc	2.5	2.5	2.5	2.5
Magnesium stearate	2.5	2.5	2.5	2.5
Batch Containing HPMC K15M				
Verapamil HCI	120	120	120	120
HPMCK15M	48	72	96	120
MCC PH101	64.5	40.5	16.5	-
PVP K30	12.5	12.5	12.5	12.5
Talc	2.5	2.5	2.5	2.5
Magnesium stearate	2.5	2.5	2.5	2.5
Batch Containing HPMC K100M				
Verapamil HCI	120	120	120	120
HPMC K100M	48	72	96	120
MCCPH101	64.5	40.5	16.5	-
PVP K30	12.5	12.5	12.5	12.5
Talc	2.5	2.5	2.5	2.5

Viscosity studies of chitosan and carrageenan: A 1% w/v solution of chitosan was prepared in 3% v/v acetic acid and 1% w/v solution of carrageenan was prepared in distilled water. The viscosity of solutions was measured using Brookefield viscometer. Various combinations of chitosan and carraggenan in ratios 1:9 to 9:1 respectively were prepared in 3 %v/v acetic acid to identify the optimum ratio for interaction of two polymers. The viscosity of solutions was measured and the ration of chitosan and carrgeenan showing the maximum viscosity was chosen for the development of sustained release tablets.

Interaction study of chitosan and carrageenan: A 1% w/v solution of chitosan was prepared in 3% acetic acid and it was dried in oven to obtain the film. Similarly, 1% w/v solution of carrageenan was prepared and dried to obtain the film. The solution of chitosan and carrageenan in 1:9 ratio in 3% acetic acid was prepared and dried to obtain the film. The dried samples of chitosan, carrageenan and their interacted sample was subjected to analysis by FT-IR spectroscopy, differential scanning calorimetry (DSC) and x-ray diffraction spectroscopy (XRD).

Development of sustained release tablets of Verapamil HCL using interaction of chitosan and carrageenan: The verapamil HCI, carrageenan, chitosan, microcrystalline cellulose PH 101 were sifted and mixed well. The blend was granulated using absolute ethanol as granulating solvent. The granules were air dried and passed through 16# sieve. The fines were separated from the granules and lubricated with magnesium stearate and talc. The granules were added to the lubricated fines, mixed well and compressed using 8 mm standard biconvex punches at a hardness of 2 to 2.5 kg/cm2.

Table 2: Formulation of Verapamil HCI sustained release tablets using carrageenan and chitosan

Name of ingredient	Fl	F2	F3	F4
Verapamil HCI	120 %	120 %	120 %	120 %
Chitosan	4.8%	7.2%	9.6%	12%
Carrageenan	43.2	64.8	86.4	108
MCC PH 101	77	53	29	5
Magnesium stearate	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5

Evaluation of Tablets: The prepared sustained release tablets of verapamil HCI were evaluated for various parameters such as thickness, weight variation, hardness, friability.

- **Drug Content:** Five tablets were weighed and powdered. The quantity of powder blend equivalent to 120 mg of verapamil HCI was weighed accurately and taken in 100 ml volumetric flask. To it 50 ml of pH 1.2 buffers was added, made up to 100 ml with water, and filtered. 2 ml of above solution was diluted to 100 ml in a volumetric flask and the drug concentration was determined at 278 nm by using UV spectrophotometer.
- **Dissolution studies:** The in-vitro release of Ve^offcimif from formulated tablets was carried out in 0.1N HCI for 2 hours and continued in phosphate buffer pH 6.8 for 6 hours. The studies were performed in USP type I dissolution test at 37 ± 0.5° C and 70 rpm speed. Samples were taken at hourly interval and analyzed for verapamil HCI content at 278 nm by using UV visible spectrophotometer.
- **Drug release mechanism study:** The in-vitro dissolution data obtained was subjected to different kinetic treatments (Zero order, First order, Higuchi and Hixson-Crowell). The results were shown in figure 3, 4, 5 and 6. The coefficient of determination (R2) was considered as main parameter for interpreting the release kinetics.

Results and Discussion: The present study was aimed to develop sustained release tablets of verapamil hydrochloride using synthetic gums like HPMC K4M, K15M and 100M and using interaction of natural gums like carrrageenan and chitosan for better control of drug release. From the viscosity studies, the 1:9 ratio of chitosan : carrageenan was found to be the optimum ratio since it has shown the maximum viscosity and hence 1:9 ratio was selected for development of sustained release tablets. All the formulations were evaluated for physical properties and *in-vitro* drug release studies. The concentration and absorbance values of vepapamil HCI in pH 1.2 buffer and in pH 6.8 phosphate buffer shown linear relationship at 278 nm (Figure 1 and 2). The correlation coefficient values for 1.2 buffer and pH 6.8 phosphate buffer was found to be 0.9991 and 0.9993 respectively.

Figure 1: Calibration curve of verapamil HCl in pH 1.2 buffer

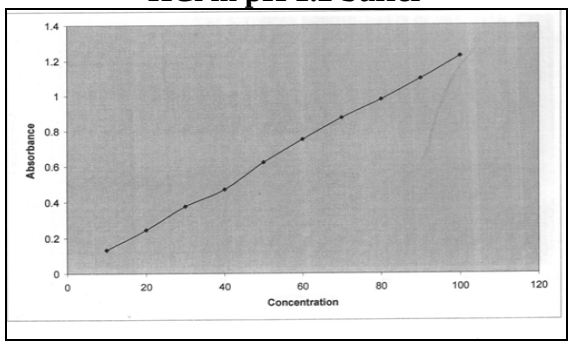
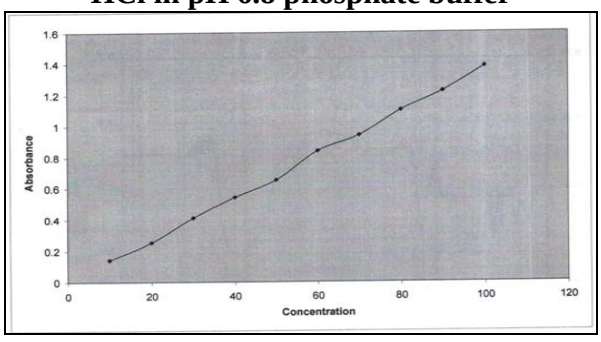


Figure 2: Calibration curve of Verapamil HCl in pH 6.8 phosphate buffer



Interaction studies of carrageenan and chitosan

1) FT-IR spectroscopy

Figure 3: FT-IR spectrum of carrageenan and chitosan interacted sample

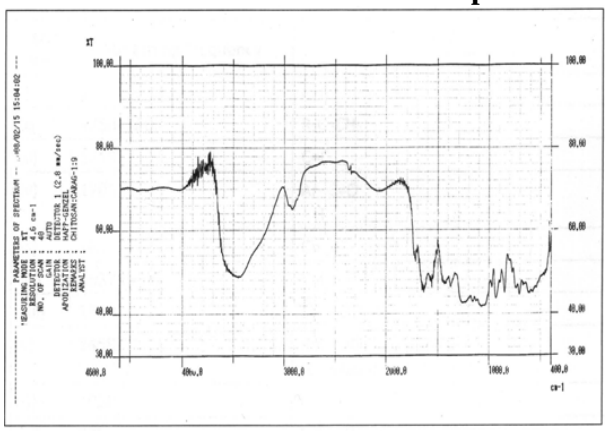


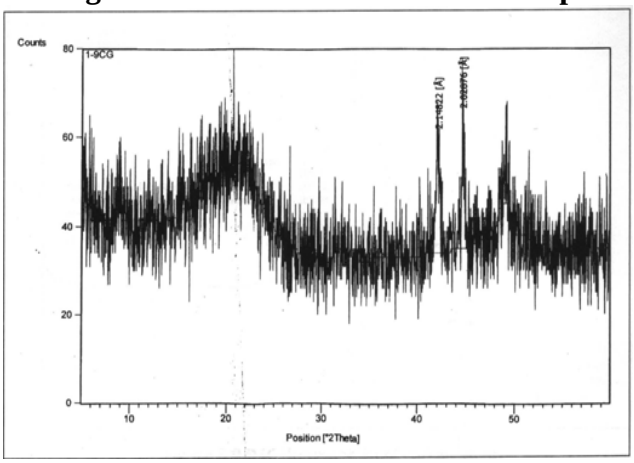
Table 3: Absence of FT-IR stretching frequencies due to interaction of chitosan and carrageenan

Stretching Frequency (cm"1)	Functional Group
1473	C=C
1458	c=c
1370-1380	C-H bending vibrations
1252	C-0
1159	C-O
1072	C-0
891	R2C=CH2 vinylidene

The FT-IR spectra and stretching frequencies due to interaction of carrageenan and chitosan were shown in figure 3 and table 3 respectively. From the data, it was observed that following stretching frequencies due to C=C at 1473 and 1456 cm"1, C-H bending vibrations at 1370-1380 cm"1, C-O stretching vibrations at 1252, 1159, 1072, and 891 cm"1 were not observed in case of the interacted sample of carrageenan and chitosan. But the above stretching frequencies were observed in case of the FT-IR spectrum of chitosan. Hence, it may be concluded that the C=C, C-H, C-O functional groups might be involved in interaction of carrageenan and chitosan as it was evidenced from the viscosity studies of carrageenan and chitosan.

2) X-ray diffraction spectroscopy

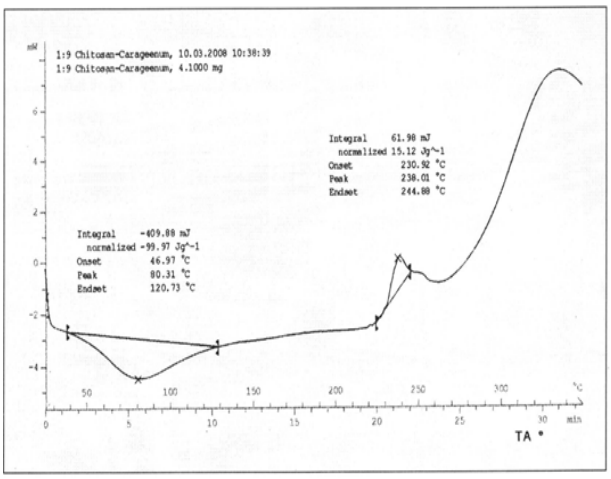
Figure 4: X-ray diffraction pattern of carrageenan and chitosan interacted sample



The x-ray diffraction pattern has shown the diffused pattern indicating the amorphous nature of the polymers. To confirm the structural changes due to interaction of carrageenan and chitosan, the x-ray diffraction pattern of the interacted sample was recorded and it was shown in figure 4. It has also shown the diffused pattern indicating the interacted polymer sample was present in the amorphous state.

3) Differential scanning calorimetry (DSC)

Figure 5: DSC thermogram of carrageenan and chitosan



The DSC thermogram of interacted sample of carrageenan with chitosan was shown in figure 5. The interacted sample of carrageenan and chitosan had shown an endothermic transition at 81.29°C with a heat content of (-) 99.97 J/g. The heat content of the system from (-) 554.90 J/g, it was in case of carrageenan (-) 212. 90 J/g and in case of chitosan was decreased to (-) 99.97 J/g. The decrease in the heat content might be due to interaction of carrageenan and chitosan.

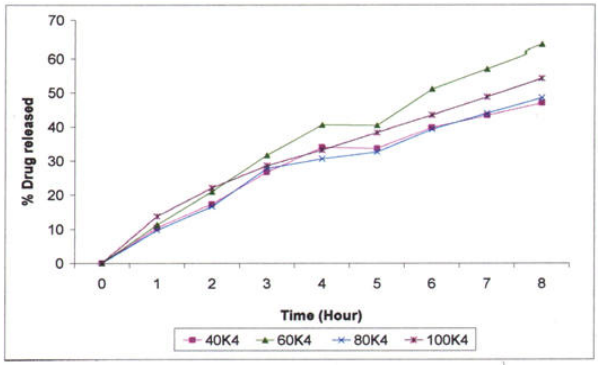
The sustained release tablets of verapamil HCI were evaluated for various parameters such as thickness, weight variation, hardness, friability, drug content, also evaluated by dissolution studies and drug release mechanism study. The prepared tablets were uniform in weight and tablet weights, also uniform in thickness and diameter and were found to be within the pharmacopeial limits. Hardness of tablets was found to be in the range of 2 to 2.5 Kg/cm2; this was within the range that ensures good handling characteristics for all batches. Friability values were found to be within acceptable limits and drug content in the tablets was found to be within 90-110%. Hence, all the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Dissolution studies

1) Dissolution studies of verapamil HCI sustained release tablets containing HPMC K4M

As shown in figure 6, the verapamil HCI tablets containing 40, 60, 80 and 100% HPMC K4M as compared to drug amount has shown 17 to 22% drug release in first 2 hours in pH 1.2 phosphate buffer. Also, no significant difference was observed in drug release when the HPMC K4M proportion was increased from 40 to 100% of drug proportion. In the dissolution studies in pH 6.8 phosphate buffer for 3 to 8 hours, 47.05, 62.90, 48.57 and 54.17 % drug release was observed in the formulation batches containing 40, 60, 80 and 100% HPMC K4M as compared to drug amount.

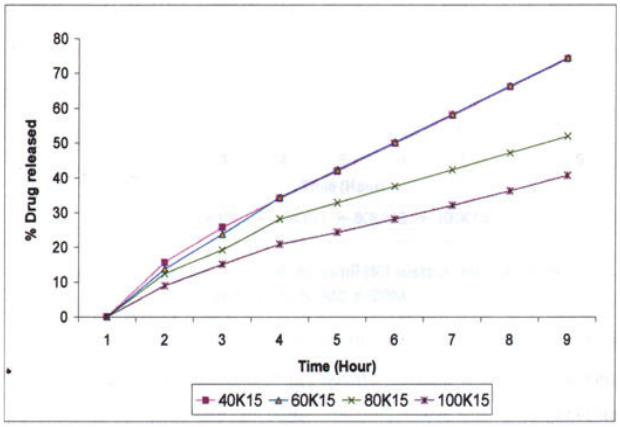
Figure 6: Drug release profile of verapamil HCI sustained release tablets containing HPMC K4M



2) Dissolution study of verapamil HCI sustained release tablets containing HPMC K15M

As shown in figure 7, the verapamil HCI tablets containing 40, 60, 80 and 100% HPMC K15M as compared to drug amount has shown 25 to 15% drug releases in first 2 hours in pH 1.2 phosphate buffer. The drug release was found to decrease from 25.76 to 15.10% as the proportion of HPMC K15 M was increased from 40 to 100 % of drug amount used in the formulation of tablets. In the dissolution studies in pH 6.8 phosphate buffer for 3 to 8 hours, 74.09, 74.40, 51.86 and 40.59 % drug release was observed in the formulation batches containing 40, 60, 80 and 100% HPMC K15M as compared to drug amount.

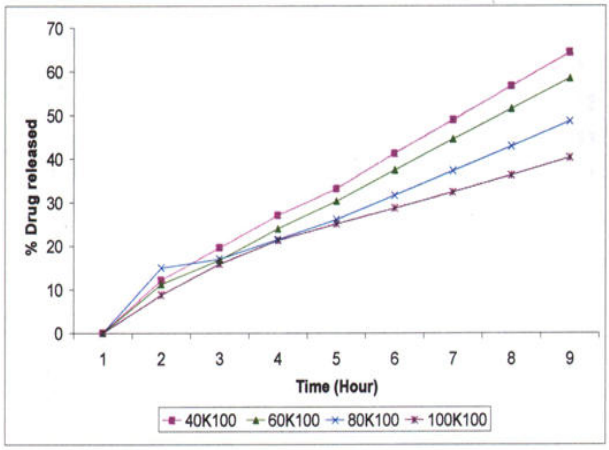
Figure 7: Drug release profile of verapamil HCI sustained release tablets containing HPMC K15M



3) Dissolution studies of verapamil HCI sustained release tablets containing HPMC K100M

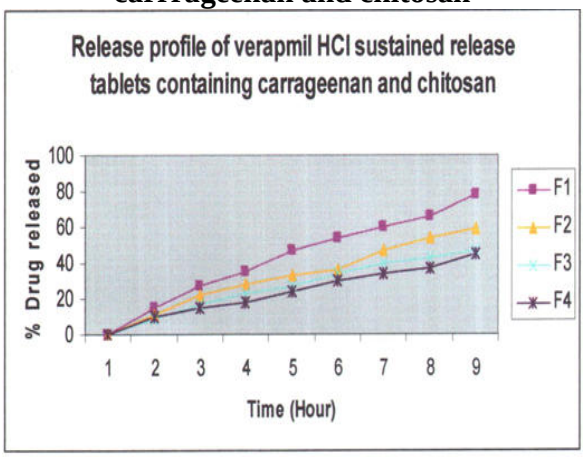
As shown in figure 8, the verapamil HCI tablets containing 40, 60, 80 and 100% HPMC K100M as compared to drug amount has shown 19 to 15% drug releases in first 2 hours in pH 1.2 phosphate buffer. The drug release was found to decrease from 19.63 to 15.84% as the proportion of HPMC K100M was increased from 40 to 100 % of drug amount used in the formulation of tablets. In the dissolution studies in pH 6.8 phosphate buffer for 3 to 8 hours, 64.31, 58.37, 48.62 and 40.22 % drug release was observed in the formulation batches containing 40, 60, 80 and 100% HPMC K100M as compared to drug amount.

Figure 8: Drug release profile of verapamil HCI sustained release tablets containing HPMC K100M



4) Dissolution study of verapamil HCI sustained release tablets containing carrrageenan and chitosan: The formulation batches containing 1:1 ratio of drugxarrageenan and drug: chitosan have shown complete drug release within first hour. As shown in figure 9, the verapamil HCI tablets containing 40, 60, 80 and 100% carrageenan and chitosan in 1:9 ratios as compared to drug amount has shown 10 to 15% drug release in first 2 hours in pH 1.2 phosphate buffer. The drug release was found to decrease from 15 to 10.47% as the proportion of carrageenan and chitosan proportion in 1:9 ratios was increased from 40 to 100 % of drug amount used in the formulation of tablets. In the dissolution studies in pH 6.8 phosphate buffer for 3 to 8 hours, 77.54, 59.36, 47.28 and 45.33 % drug release was observed in the formulation batches containing 40, 60, 80 and 100% carrageenan and chitosan in 1:9 ratio as compared to drug amount.

Figure 9: Drug release profile of verapamil HCI sustained release tablets containing carrrageenan and chitosan



Conclusion: The sustained release tablets of verapamil HCI were developed using synthetic hydrocolloids like HPMC K4M, K15M and K100M and using interaction of natural gums like carrrageenan and chitosan for better control of drug release. The post compression properties were performed for all the formulations, which include hardness, friability, thickness, weight variation and the formulations were found to be within limits. The *in vitro* drug release profile of various formulations was performed and compared. In pH 1.2 buffer Peppas model was found to be the best fit model of drug release. From the dissolution studies, it was observed that a better control on drug release can be obtained by varying the proportion of HPMC K4M, K15M and K100M. Hence, the present study concluded that the drug release can be effectively controlled for a highly water soluble drug verapamil HCI using

synthetic hydrocolloids and interaction of natural gums carrageenan and chitosan.

Acknowledgement: We are deeply indebted and grateful to Nicolas piramal India Ltd, Mumbai for providing gift sample of pure drug. We are deeply thankful to the administration of Department of pharmaceutical Sciences, Nagpur University, Nagpur, Maharashtra, for granting us permission and encouragement to utilize the facilities in the college premises and support to bring this research in an effective way.

Refernces

1. Gudsoorkar VR, Rambhau D. Influence variable of process one standard drug release from disintegrating sustained release Ibuprofen beads. The Eastern Pharmacist 1997;40(2):111-113.
2. Madhusudan Rao Y., formulation and Evaluation of Diclofenac sodium using Hydrophilic Matrices, Drug Dev, Ind. Pharm. 2001;27(8):760.
3. Siddique S, Bose A, Khanam, J. Modulation of drug (metoprolol succinate) release by inclusion of hydrophobic polymer in hydrophilic matrix. Drug Dev Ind Pharm 2011;37(9):1016-1025.
4. Deore RK, Kavitha K, Tamizhmani TG. Preparation and evaluation of sustained release matrix tablets of tramadol hydrochloride using glyceryl palmitostearate. Trop J Pharm Res 2010;9(3):275-281.
5. Shargel L. (Ed.), Pharmacy Review. A Wiley Medical Publication, Singapore, 1990, pp. 33-54.
6. Gennaro A.R. Remington's Pharmaceutical sciences, Mack publishing company, Easton, Pennsylvania. 17th edn 1985; 619-652:1644-1660.
7. Marwa et al. Formulation and evaluation of verapamil hydrochloride buccoadhesive tablets. UJPB 2013; 01(03):48-57.
8. Reynolds JEF. Martindale, The Extra Pharmacopoeia, Vol. 33, The Royal Pharmaceutical Society, Great Britain, London 2002; 989-991.
9. Buzinkaiova T, Skacani I, Netriova J. Quantitative assay of verapamil in drugs and serum by capillary isotachophoresis. Pharmazie, 1995;50:799–800.
10. Clarke EG. Isolation and identification of drugs, London, The pharmaceutical press. 2004; 1695-1697.
11. Harder S, Thurmann P, Siewert M, Blume H, Huber TH, Rietbrock N. Pharmacodynamic profile of verapamil in relation to absolute bioavailability: investigations with a conventional and controlled release formulation. J Cardiovasc Pharmacol 1991;17:207–212.
12. Elkheshen SA. Bioadhesive matrix as controlled release dosage form for verapamil hydrochloride. Pharm Ind 1998;60:555–559.
13. Jankowski A, Marzec A, Lamparczyk H. Comparative bioavailability of verapamil from rapidly absorbed and slow release preparations. J Pharm Biomed Anal 1991;10:1101–1103.
14. Ahmed JH, Merdith PA, Ellott HL. The influence of age on the pharmacokinetics of verapamil. Pharmacol Res 1991;24(3):227-233.
15. Longer MA, Ch'ng HS, Robinson JR. Bioadhesive polymers as platform for oral controlled drug delivery. J Pharm Sci 1985; 74:406-411.