Research Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2015, Volume 3, Issue 2
ISSN: 2321–3647(online)

Development Of pH Sensitive Hydrogel for Intestinal Delivery of Amoxicillin Trihydrate using Carbopol-PEG400

Priyeshnath D. Rathod*[1], Sudhir P. Dabke[1], Malvika A. Safaya[1]
1. *Department Of Chemical Engineering, The Maharaja Sayajirao University of Baroda*

ABSTRACT

A pH sensitive hydrogel using Carbopol-PEG 400 combination was prepared and loaded with amoxicillin trihydrate drug to study its sustained release. The hydrogel prepared was of physical nature. Two types of hydrogel were prepared with and without drug. The drug used was amoxicillin trihydrate. This drug is used to treat peptic ulcer in gastrointestinal tract. This drug becomes unstable in acidic environment of stomach. A pH sensitive hydrogel can be designed which can retain the drug in the polymer core at low pH values and release it at high pH value environment like gastrointestinal tract. Characterization of the hydrogel was done by SEM and FTIR and performance was studied by swelling method and in vitro drug release. FTIR studies gave the backbone structure of hydrogel carrying the drug. The surface morphology study by SEM showed that the prepared hydrogel was porous in nature. The swelling studies showed that the hydrogel swelled more in basic medium as the components were anionic in nature. The release profile showed 83.93% sustained drug release after 10hours. The carbopol-PEG400 hydrogel is suitable for the delivery of amoxicillin trihydrate as the drug is not stable in the stomach and can be delivered satisfactorily to the intestine where the pH is favourable.

Keywords: Carbopol 934P, PEG-400(Polyethylene glycol), Hydrogel, Intestinal drug delivery, sustained release

*Corresponding Author Email: priyeshnath23@yahoo.com
Received 23 January 2015, Accepted 10 February 2015

Please cite this article as: Rathod PD *et al.*, Development Of pH Sensitive Hydrogel for Intestinal Delivery of Amoxicillin Trihydrate using Carbopol-PEG400. American Journal of Pharmacy & Health Research 2015.

INTRODUCTION

In a simple binary system of a polymer and a liquid, a sol is formed when the polymer–liquid interaction are more favoured, than both polymer–polymer and liquid–liquid interactions. If the polymer is hydrophilic and the liquid is water, the product of the polymer–liquid interaction is called a hydrosol. A cross-linked hydrosol is called a hydrogel and can only swell in the surrounding liquid to a certain swelling ratio, depending on the number of crosslinks, i.e., the crosslinking density. The terms gels and hydrogels are used interchangeably by food and biomaterials scientists to describe polymeric cross-linked network structures.[1] The term hydrogel describes three-dimensional network structures obtained from a class of synthetic and/or natural polymers which can absorb and retain significant amount of water. These hydrogels can swell, or deswell in response to changes in pH, temperature, ionic strength, and electromagnetic radiation.[2]

Carbopol is made of carbomers. Carbopol polymers are acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. Carbomers readily absorb water, get hydrated and swell. In addition to its hydrophilic nature, its cross-linked structure and it's essentially insolubility in water makes Carbopol a potential candidate for use in controlled release drug delivery system. Carbomer polymers are cross-linked together and make a microgel structure that makes them optimal to be used as a drug vehicle for dermatological purposes. They can be used in cases when drug delivery in a controlled manner is desired. The microgel structure makes it possible for these systems to tolerate the physical movement of the body and shape themselves after the application area movement.[3]

Polyethylene glycol is known as hydrophilic monomer which provides distinct advantage in both fabrication and application of hydrogels. PEG is known for its stealth properties, that is once its attached to certain formulations, it allows slow release of the formulation, thus enabling controlled release, as well as reduce uptake of harmful immunoglobins. PEG is non-toxic, thus ideal for biological applications, and can be injected into the body without adverse effects. It is also an FDA approved materials for use in humans.[4] Poly(ethylene glycol) (PEG) is also used in many biomedical applications due to of its outstanding physico-chemical and biological properties such as hydrophilicity, biocompatibility, and lack of toxicity.[5]

pH dependent hydrogels exhibit swelling behaviour as they contain ionisable side or pendant groups like carboxylic acid(acidic) and amine(basic). In a medium of optimum pH and ionic strength, the pendant groups ionize and develop fixed charges on the gel and also swelling force

in the gel. This swelling force increases in the gel due to localization of fixed charges on the pendant group and as a result, the mesh size of the network changes with small change in pH.[6] The drug used in the current study was amoxicillin trihydrate. This drug is unstable in the acidic environment of stomach and so there is need to protect the drug and release in the later part of gastrointestinal tract. For this purpose, we prepared and evaluated a pH sensitive hydrogel of Carbopol-PEG400.

MATERIALS AND METHODS

Carbopol 934 was obtained from Shreeji Pharma International, Baroda. Polyethylene glycol (PEG) 400 was obtained from Pharmacy department of M.S.University of Baroda. Amoxicillin Trihydrate was purchased in API form commercially from Vadodara. All other reagents used were of analytical grade.

Preparation of hydrogels

1% (w/v) hydrogel was prepared by taking 1gm of carbopol in 100ml of distlled water. This mixture was stirred for 24hours but the hydrogel didn't form. Only lumps were observed. Then a 2% (w/v) hydrogel was prepared by mixing 0.6gram of carbopol 934P in 30ml of distilled water. This solution was stirred on magnetic stirrer. Then 3ml of PEG400 was added and this solution was stirred for 24hours. After 24hours, a highly viscous solution was formed. This viscous solution was poured on petridish and was placed in vacuum dryer for one day and a thin film of carbopol-PEG was obtained. A 3% (w/v) hydrogel was prepared by taking 0.9gm of carbopol and 45ml of water in quantities and above procedure was repeated. But again only lumps were formed. Another hydrogel was prepared in the same manner but it was loaded with 500mg of amoxicillin trihydrate during stirring process. So a hydrogel with drug was obtained. The dried hydrogel was crushed and used for further studies.

Table 1: Formulation chart of hydrogel with and without amoxillicin trihydrate

Sr.No.	Ingredient	Hydrogel without drug (1% w/v)	Hydrogel with drug(2%w/v)	Hydrogel without drug(2%w/v)	Hydrogel without drug(3%w/v)
1.	Carbopol 934P	1gm	0.6gm	0.6gm	0.9gm
2.	Water	100ml	30ml	30ml	45ml
3.	PEG	-	3ml	3ml	-
4.	Amoxicillin trihydrate	-	500mg	-	-

Swelling Studies

The pH dependent swelling property of the hydrogels was studied in both 1.7pH of 0.1N HCl acidic medium and 7pH of distilled water basic medium. 20mg of hydrogel without drug was

placed in 30ml solution of HCl and water for time interval of 10mins till 1hour. At every 10minute interval, the hydrogels were removed and excess surface liquid was removed by blotting paper and their weights were recorded. Another study was carried out by taking 39mg of hydrogel without drug and the same process was repeated with 1 hour of time interval for 5hours.

The percentage swelling (S) was determined by the following equation,

$$S = \frac{(weight of\ swollen hydrogel - weight of\ dry hydrogel) \times 100}{weight of\ swollen hydrogel}$$

Drug Content

Amoxicillin trihydrate (100mg) was dissolved in 100ml volumetric flask with 0.1N HCl(1mg/ml). Here, 0.1N HCl is taken as standard medium. This solution is taken as stock solution. This stock solution (100µg/ml) was further diluted with 0.1N HCl to obtain solution of 50 to 300(µg/ml). By withdrawing 0.5ml stock solution and volume makeup upto 10ml with 0.1N HCl in 10ml volumetric flask, it produced 50(µg/ml) solution.After that, the absorbance is measured in Perkin Elmer's LAMBDA 25 UV/Vis spectrometer, and the spectra is scanned between 200-800nm. The characterization peak of amoxicillin trihydrate is found at 272nm. Same procedure was done to obtain solution of 100,150,200,250,300 (µg/ml) and their absorbance was found respectively.

***In vitro* drug release studies**

Drug release profiles were evaluated in vitro using a dissolution test apparatus (electro lab TDT-08L).The USP paddle method was selected to perform the dissolution profiles of amoxicillin trihydrate contained in hydrogel from UV spectrophotometer. Here 0.1 N HCl is taken as a dissolution medium.The same test for the formulation was carried out in 900 ml of 0.1N HCl, maintained at 37 ± 0.5°C at a paddle rotation speed of 50 rpm constantly.10ml sample was withdrawn at every 1hour interval up to 10 hours and the progress of the dissolution was monitored. Sample volume was replaced by fresh dissolution medium. Then the absorbance of sample solution up to 10 hours was measured by using uv-spectrometer Perkin (UV/Vis, Lambda 25).The sample solutions were analysed for amoxicillin trihydrate by UV absorbance at 272 nm using a Spectrophotometer Perkin (UV/Vis, Lambda 25). The amount of drug present in the sample was calculated from calibration curve constructed from the standard solution of amoxicillin trihydrate. Then, cumulative percentage of drug release was calculated.

RESULTS AND DISCUSSION

Scanning electron microscopy of hydrogel

The scanning electron microscopy was carried out to study the morphology,texture and porosity of hydrogel. The SEM images (Fig.1 and Fig.2) show the porosity of hydrogel and how the drug filled these pores.Even homogeneity of hydrogel with drug can be observed.

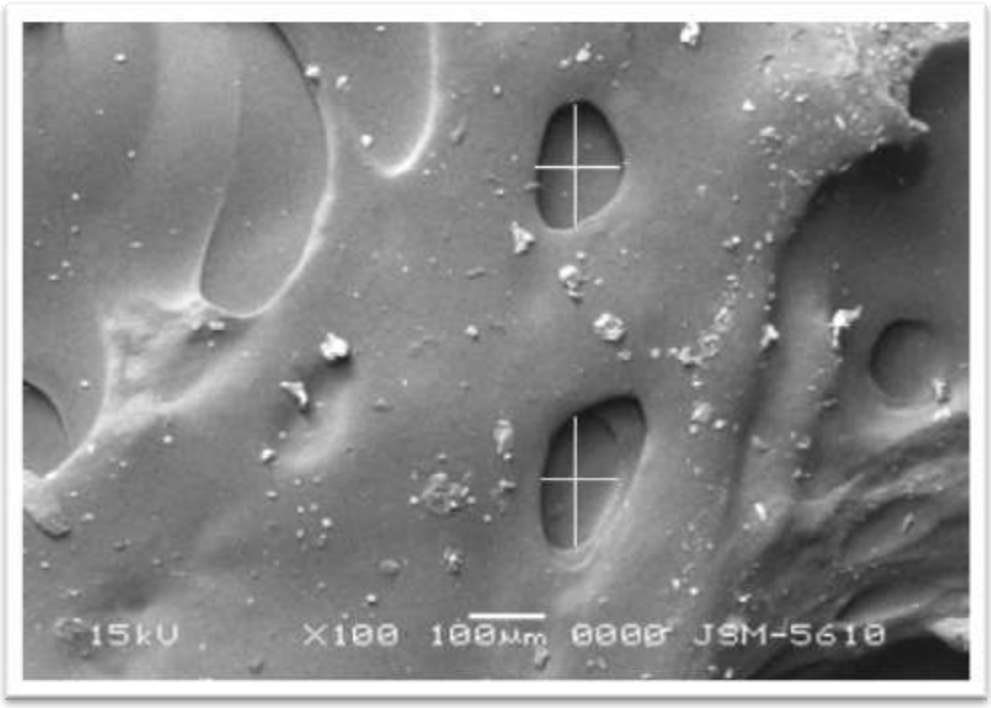

Figure.1: SEM photograph of hydrogel without drug in 100X.

Figure.2: SEM photograph of hydrogel with drug in 100X.

FT-IR analysis

FTIR studies were carried out for hydrogel with and without drug. Hydrogen bonding has a significant influence on the peak shape and intensities,generally causing peak broadening and shifts in absorption to lower frequencies. On analyzing the graphs of hydrogel with and without drug, we determine the backbone structure of hydrogel with drug. (Fig.3 and Fig.4)

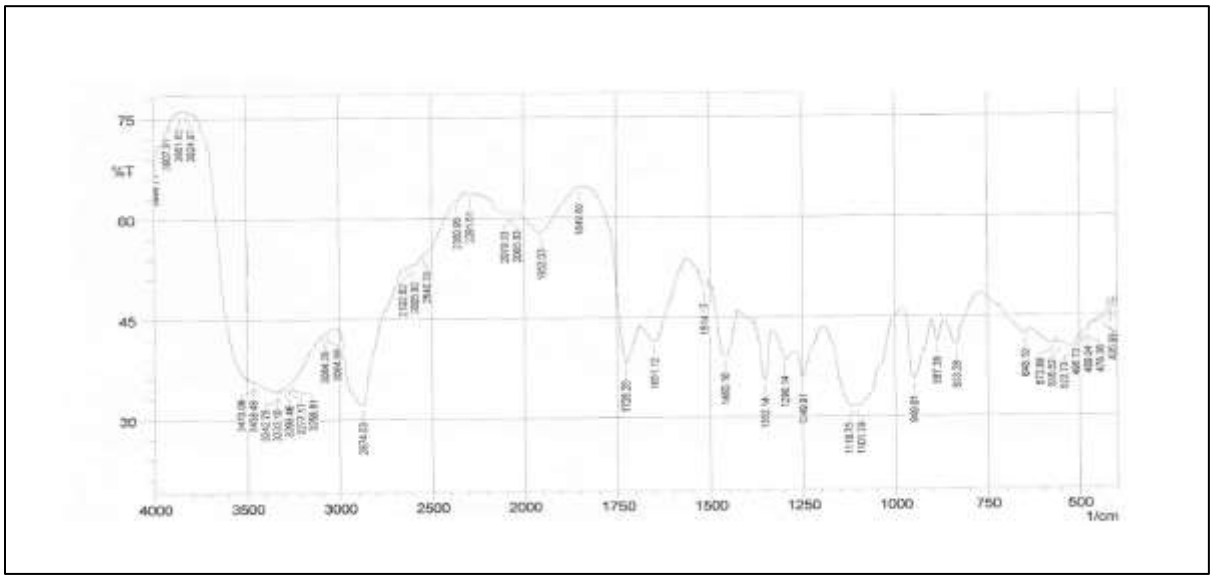

Figure.3: FT-IR spectra of hydrogel with drug

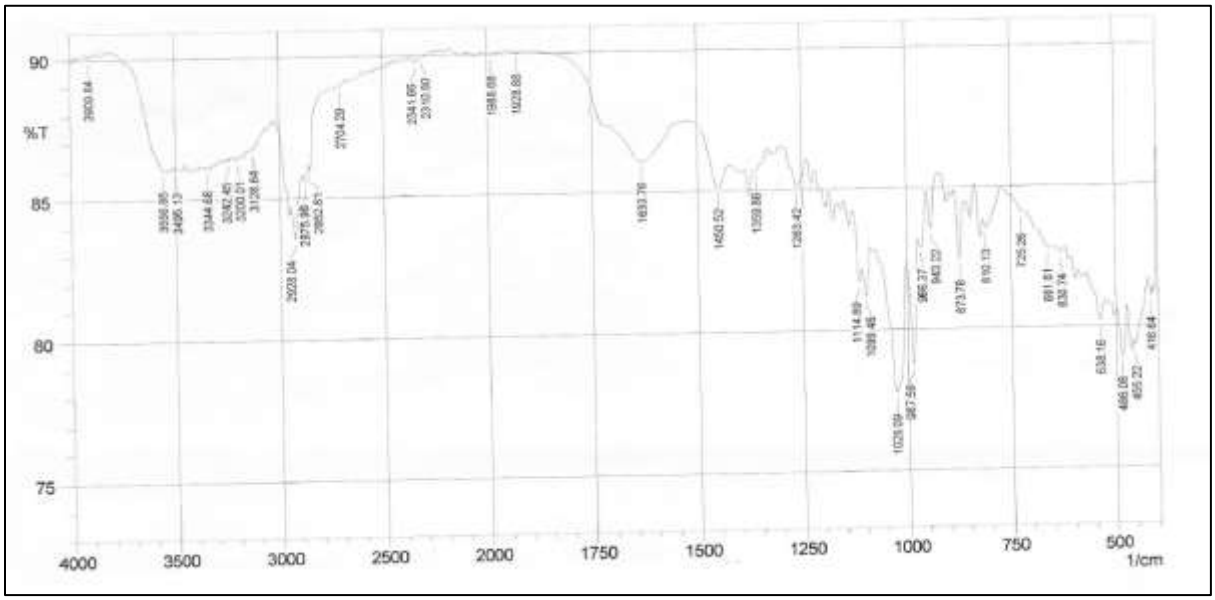

Figure.4: FT-IR spectra of hydrogel without drug

Swelling studies

It can be seen from the graphs (Fig.5 and Fig.6) hydrogel in water swells more compare to HCl, because carbopol is self - acidic and water is basic medium compare to HCl. The polymer used in this hydrogel is anionic. It will swell more in basic medium compared to acidic medium. In

case of 0.1N HCl, the hydrogel swelling pattern shows an instant increase in swelling then a constant pattern. It was observed that hydrogel kept in distilled water showed same weight after 24hours e.g. (1.034gms) in table 3 from which we can conclude that there is no deswelling till the initial weight even after 24hours. Same was observed in case of 0.1N HCl. By comparing the tables 2 and 3, it can be seen that 0.02gms of hydrogel in 0.1N HCl has swelling ratio 650 after 1hour and 0.039gms of same hydrogel has swelling ratio of 802.5 after 1hour. Same was observed for distilled water. This shows that there is no difference in swelling ratios by weight change. Most of the pH sensitive hydrogels swell at high pH values and collapse at low pH values.

Table 2: Swelling studies of hydrogel of 10minute interval

Time	Weight obtained		Swelling ratio%	
	0.1N HCl	Distilled water	0.1N HCl	Distilled water
After 10mins	0.12	0.699	500	3350
20	0.14	0.744	600	3620
30	0.15	0.875	650	4275
40	0.16	0.982	700	4810
50	0.14	0.990	600	4850
60	0.15	1.023	650	5015

Table 3: Swelling studies of hydrogel of 1hour interval

Time	Weight obtained		Swelling ratio%	
	0.1N HCl	Distilled water	0.1N HCl	Distilled water
After 1hour	0.352	1.01	802.5	2489.7
2	0.376	1.36	864.1	3387.17
3	0.379	1.55	871.7	3874.35
4	0.319	1.69	717.9	4233.33
5	0.372	1.95	853.8	4900

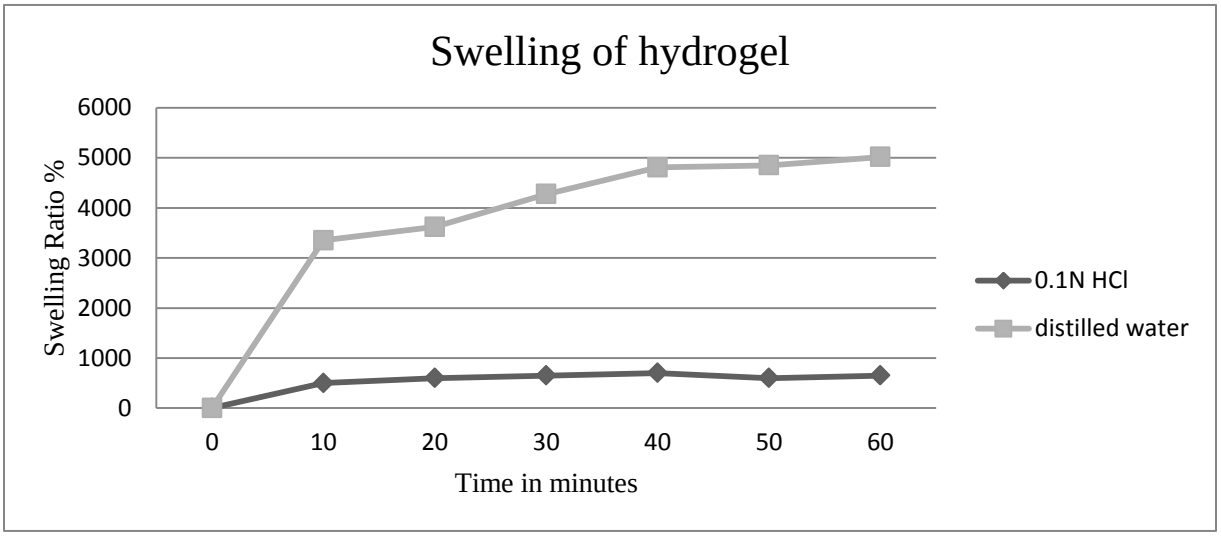

Figure. 5: Graph showing percentage swelling of hydrogel with 10minute time interval

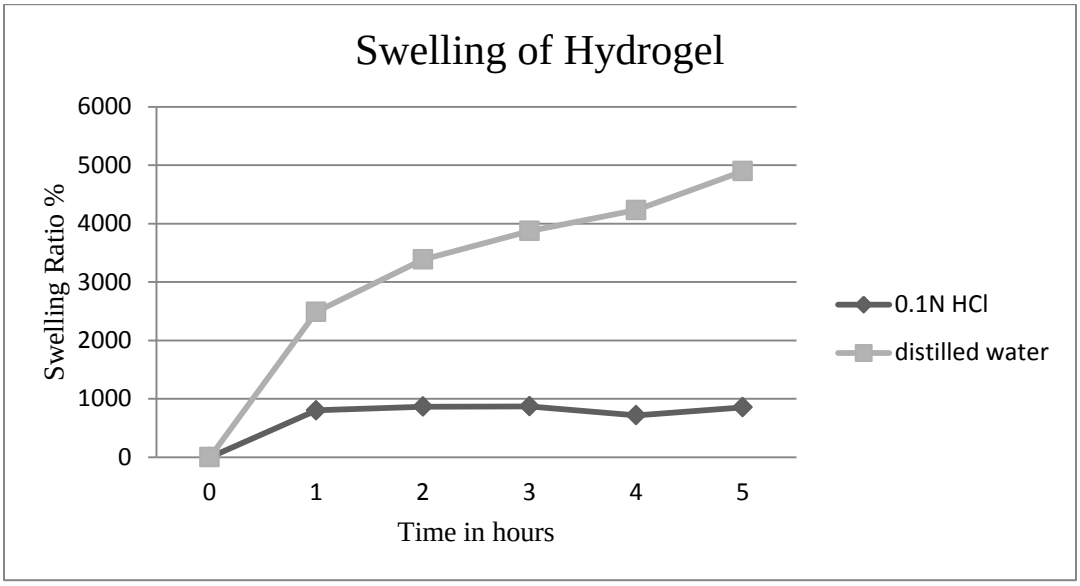

Figure.6: Graph showing percentage swelling of hydrogel with 1hour time interval

***In Vitro* Release Study**

The cumulative drug release with respect to time can be seen in the graph (Fig.7). Here, starting from 1hour, the percentage is gradually increasing up to 10 hours. At the end of 10 hours the cumulative drug release was found to be 83.93%. This showed that the hydrogel can perform sustained release of drug for long duration.

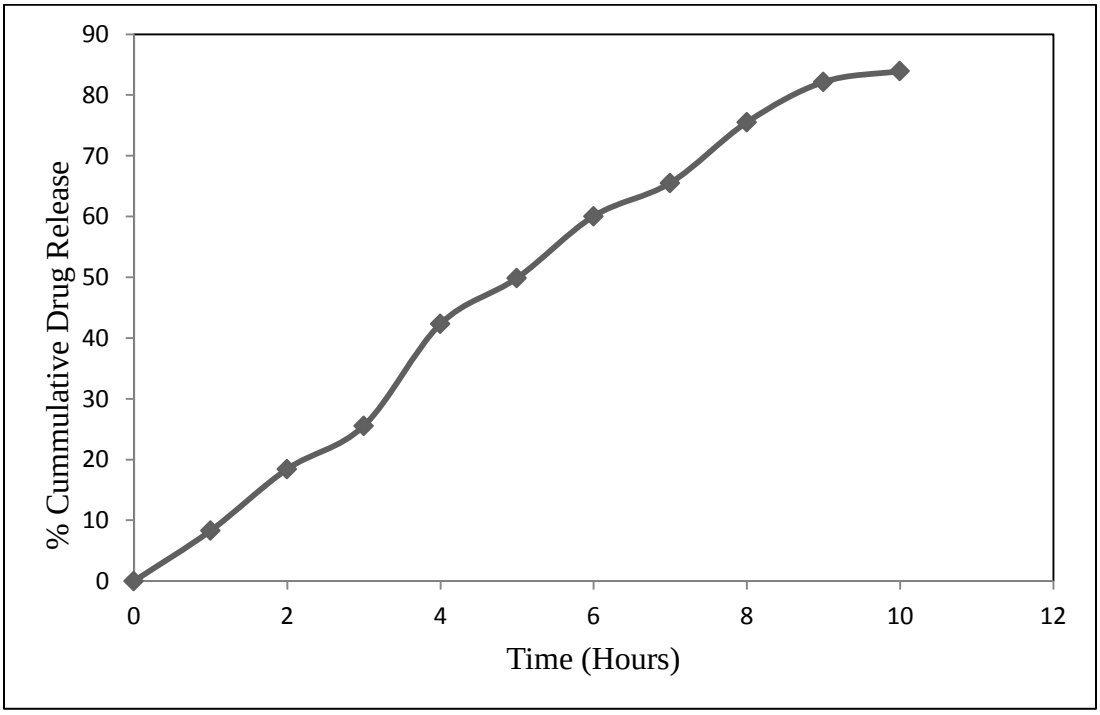

Figure.7: Graph showing percentage cumulative drug release for 10hours

CONCLUSION

From the results obtained, it may be concluded that PEG400 acts as surfactant. Carbopol 934P is having a cross-linked structure. Carbopol is anionic. A 2%(w/v) hydrogel can be prepared. By decreasing or increasing this w/v %, we were unable to prepare the hydrogel. Morphology analysis shows that hydrogel becomes a carrier for amoxicillin trihydrate since the porous nature of hydrogel holds the drug. The swelling of hydrogel was high in basic medium compared to acidic medium. Drug release studies showed sustained release of drug from hydrogel upto 83.93%. Thus hydrogel can be prepared using carbopol and PEG 400 as basic components and can be used to deliver amoxicillin trihydrate in sustained manner in the intestine and this hydrogel can be studied for compatibility with other drugs to sustain them in acidic environment of stomach and release in the intestine.

ACKNOWLEDGEMENT

The authors would also like to thank Dr. Ranjan Sengupta, Dr. Bina Sengupta and Dr. Nitin Bhate for their support as faculty of Chemical Engineering Department, Maharaja Sayajirao University of Baroda. The authors gratefully acknowledge the Maharaja Sayajirao University of Baroda, and Food & Drug Laboratory of Baroda for providing their research facilities to carry out this research.

REFERENCES

1. Omidian H, Park K. Swelling agents and devices in oral drug delivery. J Drug Deliv Sci Technol 2008;18:83-3.
2. Lin CC, Metters AT. Hydrogels in controlled release formulations: Network design and mathematical modeling. Adv Drug Deliv Rev 2006;58:1379-08.
3. Kermany BP. Carbopol hydrogels for topical administration of wounds [Masters Thesis]. University of Tromso; 2010.
4. Datta A. Characterization of polyethylene glycol hydrogels for biomedical applications [Masters Thesis]. Lousiana State University; 2007.
5. Khurma JR, Nand AV. Temperature and pH sensitive hydrogels composed of chitosan and poly(ethylene glycol). Polym Bull 2008;59:805–12.
6. Khare AR, Peppas NA. Swelling/deswelling of anionic copolymer gels. Biomaterials 1995;16:559-67.

7. Joshi GB, Singh MN, Shivakumar HG. Development of pH Sensitive Hydrogel for Intestinal Delivery of Methyl Prednisolone using Novel Chitosan Derivative. Int J Pharm Pharm Sci 2011;3:200-3.
8. Paulsson M. Control release gel formulations for mucosal drug delivery [Phd Thesis]. Uppsala University; 2001.
9. Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. Adv Drug Deliv Rev 2001;53:321–39.
10. Amin S, Rajabnezhad S, Kohli K. Hydrogels as potential drug delivery systems. Sci Res Essays 2009;3:1175-83.
11. Jiang Y, Li B, Chen X, Zhu M. Preparation and characterization of a prolonged and sustained drug delivery system: linear polyacrylamide in poly(N-isopropylacrylamide)/clay hydrogels. J Appl Polym Sci 2012;125:148–56.
12. Ninawe PR, Parulekar SJ. Drug Delivery Using Stimuli-Responsive Polymer Gel Spheres. Ind Eng Chem Res 2012;51:1741–55.
13. Ruiz-Caro R, Veiga MD, DiMeo C, Cencetti C, Coviello T, Matricardi P, Alhaique F. Mechanical and Drug Delivery Properties of a Chitosan–Tartaric Acid Hydrogel Suitable for Biomedical Applications. J Appl Polym Sci 2012;123:842–49.
14. Roy S, Pal K, Anis A, Pramanik K, Prabhakar B. Polymers in Mucoadhesive Drug Delivery System: A Brief Note. Designed monomers and polymers 2009;12:483-95.
15. Yadav KSH, Satish CS, Shivkumar HG. Preparation and evaluation of chitosan-poly(acrylic acid) hydrogels as stomach specific delivery for amoxicillin and metronidazole. Indian J Pharm Sci 2007;69:91-5.
16. Colo GD, Baggiani A, ZambitoY, Mollica G, Geppi M, Serafini MF. A new hydrogel for the extended and complete prednisolone release in the GI tract. Int J Pharm 2006;310:154–61.
17. Amin S, Rajabnezhad S, Kohli K. Hydrogels as potential drug delivery systems. Scientific Research and Essays 2009;3:1175-83.
18. CovielloT, Matricardi P, Marianecci C, Alhaique F. Polysaccharide hydrogels for modified release formulations. J Control Release 2007;119:5–24.
19. Peppas LB, Peppas NA. Equilibrium swelling behavior of pH-sensitive hydrogels. Chem Eng Sci 1991;46:715-22.

20. Guerrero DQ, Cornejo BNZ, Rondero AG, Segundo EP, Arzaluz MGN, Bravo JMC. Controlled release of model substances from pH sensitive hydrogels. J Mex Chem Soc 2008;52: 272-78.
21. Hoare TR, Kohane DS. Hydrogels in drug delivery: Progress and challenges. Polymer 2008;49:1993-7.
22. Emara LH, Abdou AR, El-Ashmawy AA, Badr RM, Taha NF, and Mursi NM. In Vitro release evaluation of gastroretentive amoxicillin floating tablets employing a specific design of the flow-through cell. Dissolution Technologies 2013;20:27-34.
23. Huda NH, Jhanker YM, Shahid-Ud-Daula AFM, Parvin MN, and Sarwar S. Comparative dissolution study of different brands of amoxicillin trihydrate capsules available in Bangladesh. S J Pharm Sci 2009;2:72-5.
24. Shahhet L, Alraghban D, Chehna DMF. Improvement of the physicochemical properties of amoxicillin trihydrate powder by recrystallization at different pH values. Int J Pharm Pharm Sci 2011;3:92-100.
25. Yadav VT, Jayswal BD, Patel KN, Patel BA, Patel PA. Formulation and Evaluation of Floating Tablet of Amoxicillin Trihydrate. International Journal for Pharmaceutical Research Scholars 2012;1:306-22.
26. Chao GT, Deng HX, Jia WJ, Huang WX, Gu YC, Tan H, et al. Preparation and Characterization of pHSensitive Semi-interpenetrating Network Hydrogel Based on Methacrylic Acid, Bovine Serum Albumin (BSA), and PEG. J Polym Res 2006;13:349-55.
27. Harsha S. Dual drug delivery system for targeting H.pylori in the stomach : Preparation and in vitro characterization of amoxicillin-loaded Carbopolnanospheres. Int J Nanomedicine 2012;7:4787-96.
28. Ravichandran P, Shantha KL, Rao KP. Preparation, swelling characteristics and evaluation of hydrogels for stomach specific drug delivery. Int J Pharm 1997;154:89-94.
29. Sjoberg H, Persson S, Caram-Lelham N. How interactions between drugs and agarose-carrageenan hydrogels influence the simultaneous transport of drugs. J Control Release 1999;59:391-400.
30. Peppas NA. Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm 2000;50:27-46.
31. Ji H. Kinetics of thermally induced swelling of hydrogels. Int J Solids Struct 2006;43:1878-1907.

32. Peppas NA, Khare AR. Preparation, structure and diffusional behaviour of hydrogels in controlled release. Adv Drug Deliv Rev 1993;11:1-35.
33. Torre PM, Enobakhare Y, Torrado G, Torrado S. Release of amoxicillin from polyionic complexes of chitosan and poly(acrylic acid) study of polymer/polymer and polymer/drug interactions within the network structure. Biomaterials 2003;24:1499–06.