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Research Article

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pH Sensitive Hydrogel Based Controlled Drug Delivery System for Oral Delivery of Famotidine

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Abstract: Improving the safety efficacy ratio of existing drugs is a current challenge to be addressed rather than the development of novel drugs which involve much expense and time. The efficacy of drugs is affected by a number of factors such as their low aqueous solubility, unequal absorption along the gastrointestinal (GI) tract, risk of degradation in the acidic milieu of the stomach, low permeation of the drugs in the upper GI tract, systematic side effects, etc. A new pH responsive drug delivery system based on inter-polymeric hydrogels was developed for oral drug delivery of famotidine, the effect of various formulation variables i.e. concentration of crosslinking agent and polymer ratio were studies on entrapment efficiency, pH sensitive behavior, temperature sensitive swelling, % swelling, mucoadhesion and in-vitro drug release profile. For the development of hydrogel formulation, the % swelling and release of drug in plays an important role. The basis on optimize the formulation. In this the polymer and crosslinker concentration varying in different ratio.

Keywords: GI tract, Hydrogel, Mucoadhesion, pH sensitive behavior

1. Introduction

Drugs can be administered through various routes; however, of all the routes of administration, oral route of administration is the most convenient for administering and for dosage adjustments. Important reason for their popularity is their convenience of application and the ease of preparation on an industrial scale. Controlled drug delivery occurs when a polymer is combined with a drug or active agent such that the release from the bulk material is pre-designed. Controlled and Sustained Release, both has been used in consistent and confusing manner. Both represent separate delivery process. Sustained release constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. Sustained release system generally don't attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order. The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and /or physiological parameters.

2. Mechanism of Controlled Drug Release Systems

Diffusion Controlled System

Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. The flux of the drug J (in amount / area -time), across a membrane in the direction of decreasing concentration is given by Fick's law.

$$J = - D \frac{dc}{dx}$$

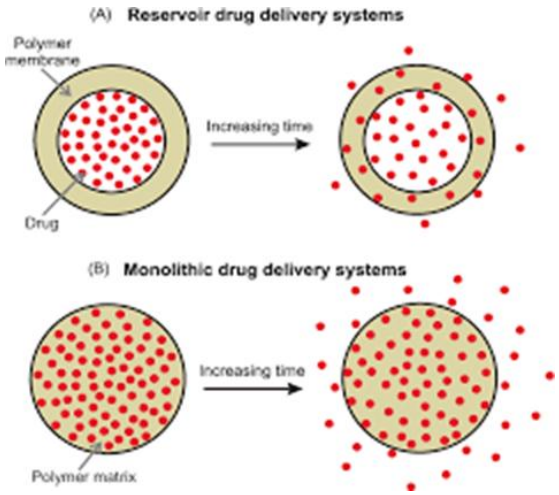
Where, D = diffusion coefficient in area/ time

dc/dx = change of concentration 'c' with distance 'x'

Diffusion systems are characterized by release rate of drug is dependent on its diffusion through inert water insoluble membrane barrier. There are basically two types of diffusion devices.

(a) Reservoir Type: In the system, a water insoluble polymeric material encloses a core of drug, which controls release rate. Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media. The polymers commonly used in such devices are Ethyl cellulose and Poly-vinyl acetate.

(b) Matrix Type: A solid drug is homogenously dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution.



Bioavailability of controlled release dosage forms:

Controlled oral drug delivery systems is the transit time through the GI tract. The average time it takes for a solid dosage form, from the time of ingestion, to reach the lower end of the tract, is 10-12 hrs. This has restricted oral delivery systems to twice-daily administration, unless the drug has a long half-life. Recent attempts to overcome this limitation include the use of special drugs such as anticholinergics, use of modified density particles and most recently, the use of bioadhesives. However, a major problem which has to be taken into consideration during the design of these systems is the ability to localize such system in selected regions of the GI tract where absorption of the drug is optimum. Many drugs have narrow windows of absorption and if the delivery system releases its drug outside this window, low bioavailability and inferior therapeutic efficacy may result.

3. An introduction to hydrogel

Hydrogels are cross linked polymer networks that can expand substantially and retain large amount of water without being dissolved. The networks are composed of homopolymers or copolymers, and are insoluble due to the presence of chemical cross links, or physical cross links, such as entanglement or

crystallites. The latter provide the network structure and physical integrity. These hydrogels exhibit a thermodynamic compatibility with water allows them swell in aqueous media.

The original hydrogel polymer i.e., a copolymer of 2-hydroxyethyl methacrylate and ethylene dimethacrylate was developed by Wichterle and Lim in 1954. The development of the first soft hydrogel contact lenses by Wichterle in 1961 represented the successful clinical application of hydrogel polymers and remains one of the most important hydrogel-based contact lenses till today. In the past few years, various hydrogel systems such as smart hydrogel, supramolecular hydrogel, shape memory hydrogel, polymer hydrogel scaffolds, injectable hydrogels, actuators, self-healing hydrogels, and injectable hydrogels have been extensively used in tissue engineering, targeted drug delivery, bone regeneration, wound injury, surgical devices, gene therapy, vaccines, immunotherapy, corneal treatment, diagnostic imaging, sensors in cancer therapy and absorbable bone plates, etc.

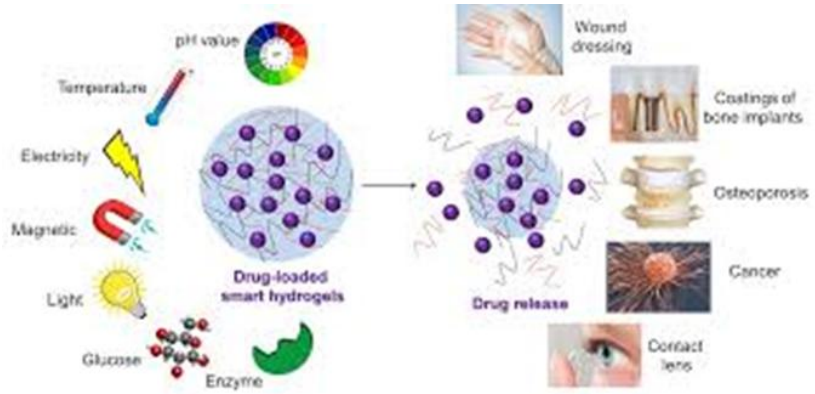


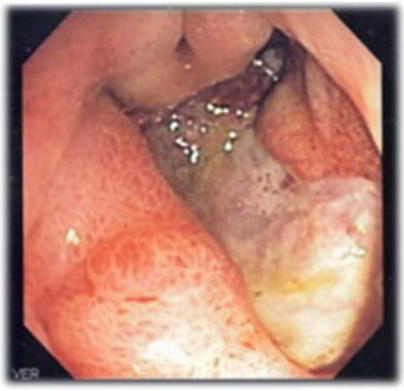
Figure 1: Smart Hydrogel for advance drug delivery

Peptic ulcer:

An ulcer is an open sore of the skin, eyes or mucous membrane, often caused, but not exclusively, by an initial abrasion and generally maintained by an inflammation, an infection and/or medical condition which impede healing. In other words, it is a macroscopic discontinuity of the normal epithelium some specific types of ulcer are peptic ulcer, mouth ulcer, stress ulcer, diabetic foot ulcer, ulcerative colitis, corneal ulcer etc.

A peptic ulcer is an ulcer of an area of the GIT that is usually acidic and thus extremely painful. It results probably due to an imbalance in the aggressive (acid, pepsin and H. pylori) and the defensive (gastric mucus, bicarbonate and prostaglandins) factor most of the peptic ulcer are usually associated with Helicobacter pylori, a spiral bacterium that thrives in the acidic environment of the stomach.

Gastric ulcer



Deep gastric ulcer

Classification: A peptic ulcer may be classified based on its location as follows,

 Gastric ulcer: These are less common and usually occur along the upper curve of the stomach.

 Duodenal ulcer: This is the most common type of peptic ulcer which occurs in the duodenum, the first few inches of small intestine just below the stomach.

 Esophageal ulcer: Repeated regurgitation of the stomach contents in to the lower part of the esophagus can cause inflammation and esophagus ulcer.

Gastro-esophageal reflux disease:

Gastro-esophageal reflux disease (GERD) is a backflow of stomach contents upward into the esophagus. The lining of the stomach protects the stomach from the effects of its own acids- because the esophagus lacks a similar protective lining, stomach acid that refluxes into it causes pain, esophagitis and damage.

Acid refluxes when the lower esophageal sphincter (LES) is not functioning properly. The force of gravity contributes to the reflux when the person is lying down. The degree of inflammation caused depends on the acidity of the stomach contents, volume of the stomach acid into the esophagus and the ability to clear the regurgitated fluid from the esophagus.

Symptoms:

• Heartburn it usually occurs after meals or while

• Regurgitation of stomach contents in to the mouth.

• Water brash: - excessive salivation occurs when stomach acid irritates the inflamed lower esophagus.

Complication:

• Peptic esophageal structure (narrowing of an area of esophagus).

• Esophageal ulcer.

• Barrett's syndrome (precancerous changes in the lining of esophagus).

Diagnosis: X-rays studies, esophagoscopy, pressure measurement of the LES, esophageal PH tests, and the Bernstein's test are some of the methods to help confirm the diagnosis and check for complications. Proof that symptoms result from acid reflux is best provided by a biopsy or the Bernstein Test, regardless of x-ray or endoscopic findings. A biopsy is also the only reliable way to detect Barrett's syndrome.

Treatment: Several measures can be taken to relieve acid reflux, some of which are:

• Raising the head of the bed about 6 inches can be kept acid flowing away from the esophagus as the person sleeps.

• Avoiding coffee, alcohol and other substances that stimulate the production of acid in the stomach.

• Administering an antacid one hour before meals and another at bedtime to neutralize stomach contents.

• Taking H2-antagonists like Ranitidine or Famotidine reduces stomach acidity.

• Avoiding specific foods like fats and chocolates ant-cholinergic drugs and smoking. All of which increase the tendency of the LES to leak.

Omeprazole and Lansoprazole are the most effective drugs for rapidly healing esophageal inflammation caused due to reflux**.**

4. Preformulation Studies

We Obtained famotidine from Ravian Life Science Pvt. Ltd. Haridwar and other components, all of which came from different sources, were analytical-grade solvents and chemicals**.**

Determination of λ_{max} of famotidine

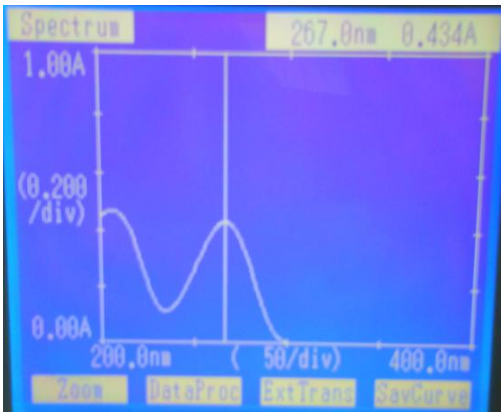


Figure 2: λ_{max} Determination of famotidine (λ_{max}-267 nm).

Determination of interference of different polymer in estimation of famotidine:

Table 1: Interference of polymers in estimation of drug.

S. No.	Description	λmax(nm)
1.	Drug	267
2.	Drug + Chitosan	267.5
3.	Drug + PVP K-90	267
4.	Drug + Acrylic acid	266.5

Preparation of standard curve

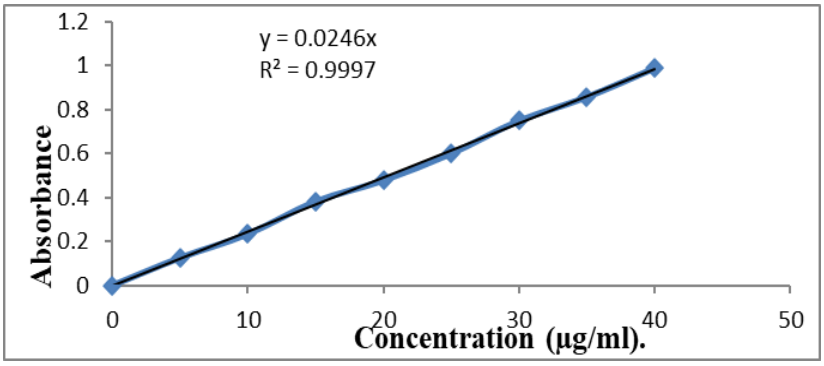


Figure 3: Standard curve of famotidine in distilled water at λmax 267 nm.

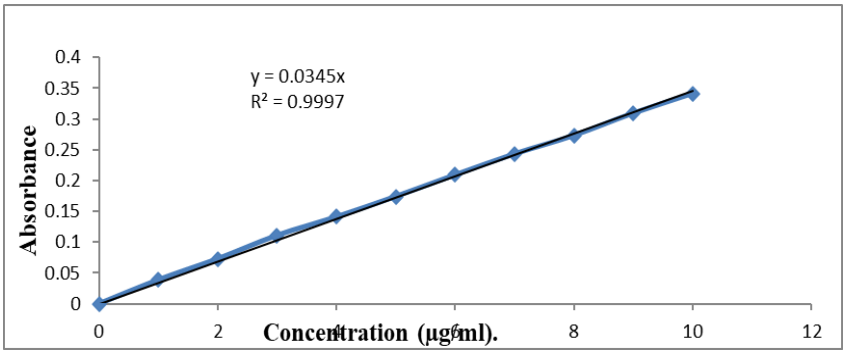


Figure 4: Standard curve of famotidine in simulated gastric fluid (pH-1.2) at λmax 267 nm.

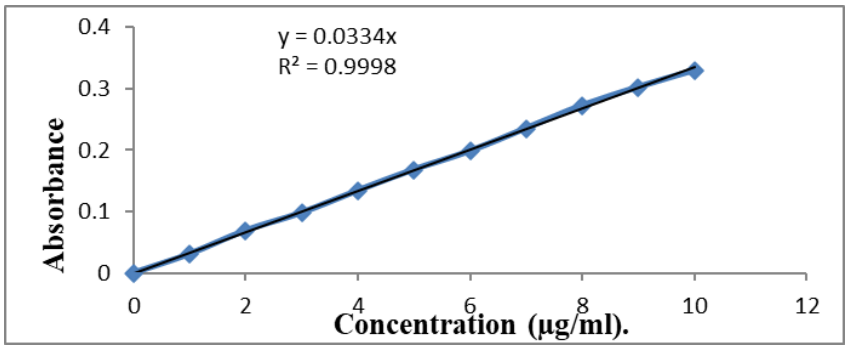


Figure 5: Standard curve of famotidine in Phosphate buffer solution (pH-7.4) at λ_{max} 280 nm.

Infrared spectrum of drug and polymers:

FTIR spectra of famotidine, from (4000-400/cm-1), was obtained using FTIR spectrophotometer (Perkin Elmer). According to Kbr pellet method and compared with standard reference spectra of famotidine.

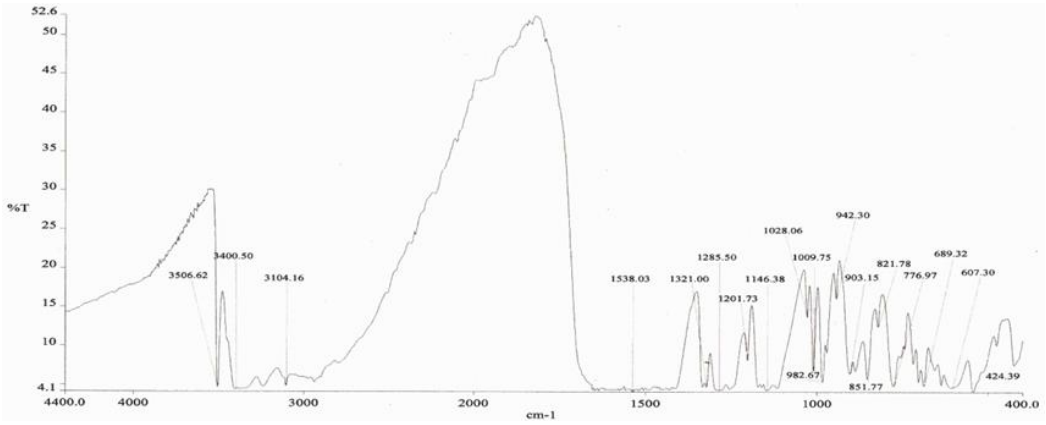


Figure 6: FTIR spectra of drug famotidine.

Table 2: Interpretation of FTIR spectra of famotidine.

S. No.	Peak(cm^{-1})	Groups
1.	3506.62	N-H Stretching
2.	1201.73	S=O Stretching
3.	1321.00	SO_2-NH_2 Stretching

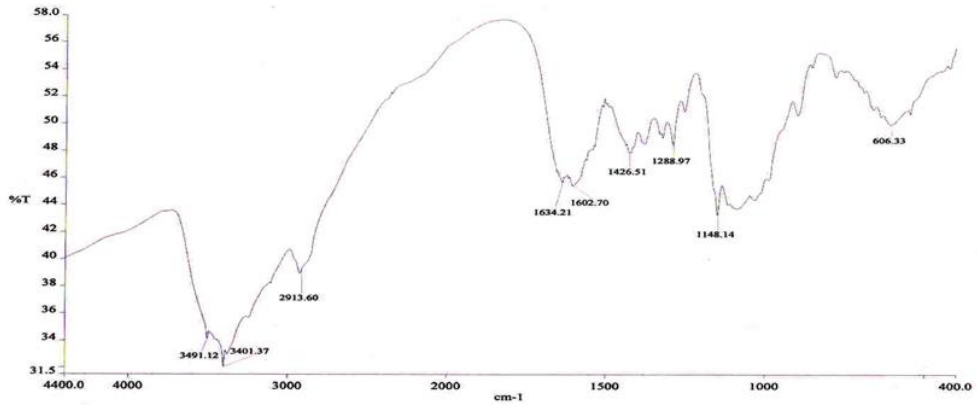


Figure 7: FTIR spectra of chitosan.

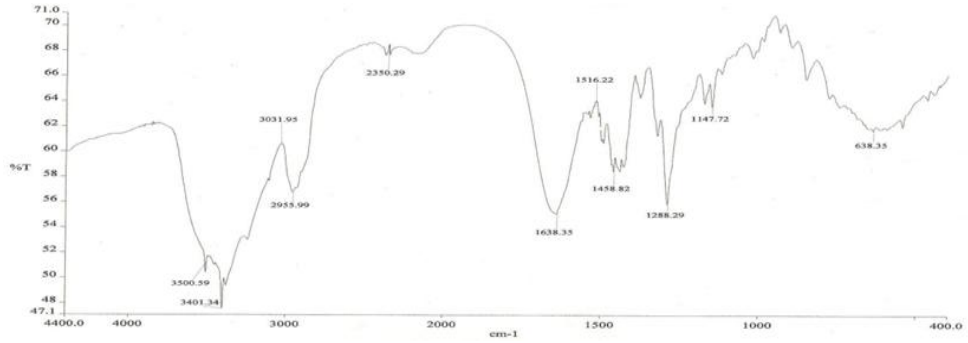


Figure 8: FTIR spectra of PVP K-90

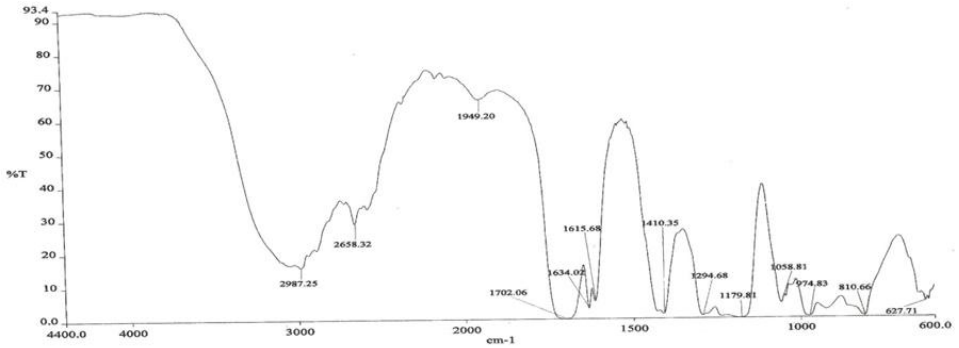


Figure 9: FTIR spectra of acrylic acid.

Drug polymer interaction study:

The drug polymer and polymer-polymer interaction study was carried out by IR spectroscopy. The IR spectrum of combination of drug and various polymers to be used in the formulation was obtained using FTIR spectrophotometer (Perkin Elmer) and compared with the individual spectra of drug and polymer to investigate any interactions.

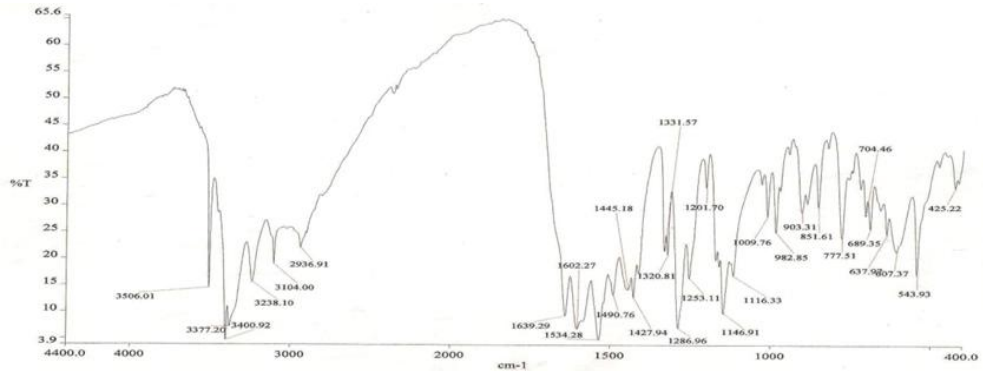


Figure 10: FTIR spectra of chitosan + drug.

Table 3: Interaction of FTIR spectra of chitosan + drug.

S. No.	Groups	Peak (cm^{-1})	
		Pure Drug	**Chitosan + Drug**
1.	N-H Stretching	3506.62	3506.01
2.	S=O Stretching	1201.73	1201.70
3.	SO_2-NH_2 Stretching	1321.00	1320.81

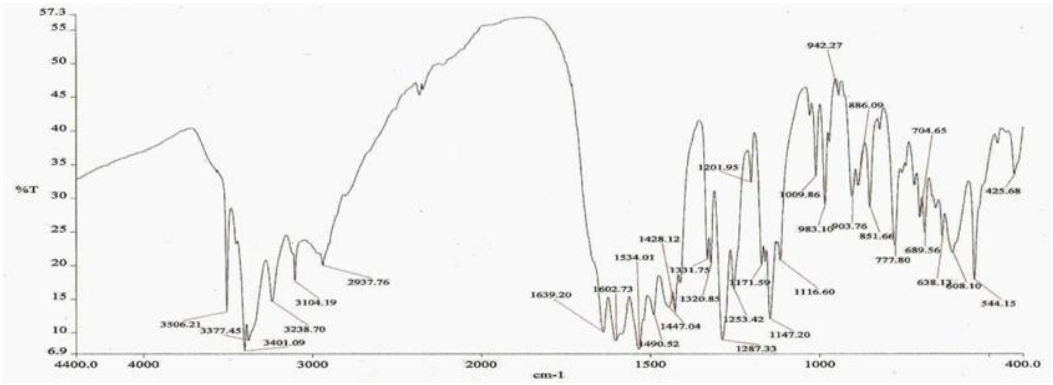


Figure 11: FTIR spectra of PVP K-90 + drug.

Table 4: Interaction of FTIR spectra of PVP K-90 + drug

S. No.	Groups	Peak (cm^{-1})	
		Pure Drug	**PVP K-90+Drug**
1.	N-H Stretching	3506.62	3506.21
2.	S=O Stretching	1201.73	1201.95
3.	SO_2-NH_2 Stretching	1321.00	1320.85

Development of hydrogel formulation

Table 5: Batch specifications of prepared hydrogel. AC1 to AC4

COMPOSITION	CHITOSAN (mg)	AAC (µl)	PVP (mg)	GLD (µl)	MBA (µl)	APS (µl)	DRUG (mg)
AC1	150	150	150	**100**	150	30	50
AC2	150	150	150	**150**	150	30	50
AC3	150	150	150	**200**	150	30	50
AC4	150	150	150	**250**	150	30	50

For the optimization of hydrogel formulation AC1 to AC4 changing the concentration of crosslinker (glutraldihyde) from 100 µl to 250 µl and keeping the concentration of Chitosan, Acrylic acid, Polyvinylpyrrolidone, N, N'-methylenebisacrylamide, Amonium persulphate are constant.

Table 6: Batch specifications of prepared hydrogel. BC1 to BC4

COMPOSITION	CHITOSAN (mg)	AAC (µl)	PVP (mg)	GLD (µl)	MBA (µl)	APS (µl)	DRUG (mg)
BC1	**200**	150	150	100	150	30µl	50
BC2	**250**	150	150	100	150	30µl	50
BC3	**300**	150	150	100	150	30µl	50
BC4	**350**	150	150	100	150	30µl	50

Table 7: Batch specifications of prepared hydrogel. CC1 to CC4.

COMPOSITION	CHITOSAN (mg)	AAC (µl)	PVP (mg)	GLD (µl)	MBA (µl)	APS (µl)	DRUG (mg)
CC1	150	150	150	100	**200**	30	50
CC2	150	150	150	100	**250**	30	50
CC3	150	150	150	100	**300**	30	50
CC4	150	150	150	100	**350**	30	50

In the hydrogel formulation CC1 to CC4 changing the concentertration of crosslinker (N, N'-methylenebisacrylamide) from 200 µl to 350 µl and keeping the concentration of Chitosan, Acrylic acid, Crosslinker (Glutraldihyde), Polyvinylpyrrolidone, Amonium persulphate are constant. The basis on in vitro release perform in SGF (pH-1.2) and optimization hydrogels formulations are obtain and the perform evaluation study of hydrogels formulations.

In-vitro drug release studies

Table 8: Comparative in-vitro drug release profile of formulations AC1, AC2, AC3 and AC4 in SGF (pH-1.2).

S. No.	Time(hr)	Comparative % drug release			
		AC1	AC2	AC3	AC4
1.	0	00.00	00.00	00.00	00.00
2.	1	10.22	8.863	6.818	4.409
3.	2	15.00	13.63	10.22	8.448
4.	3	18.40	17.40	15.20	11.337
5.	4	24.54	23.20	21.10	18.30
6.	5	33.40	31.10	29.00	25.14
7.	6	42.27	40.30	37.25	33.20
8.	7	50.45	47.35	45.23	42.10
9.	8	59.31	58.20	56.10	50.50
10.	9	66.54	63.65	60.77	56.77
11.	10	72.77	70.68	67.58	65.68
12.	11	77.90	75.80	72.70	70.68
13.	12	80.45	78.30	75.20	73.48

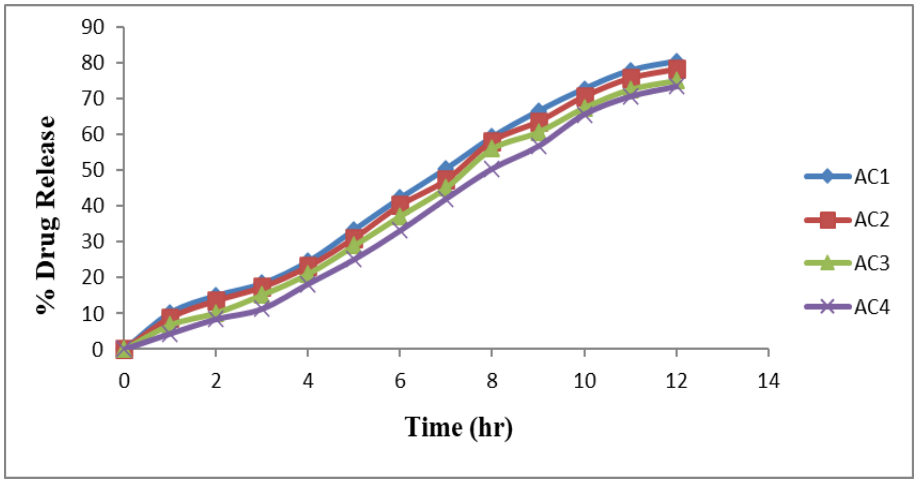


Figure 12: Comparative in-vitro drug release profile of formulations AC1, AC2, AC3 and AC4 in SGF (pH-1.2).

Table 9: Comparative in-vitro drug release profile of formulations BC1, BC2, BC3 and BC4 in SGF (pH-1.2).

S. No.	Time(hr)	Comparative % drug release			
		BC1	BC2	BC3	BC4
1.	0	00.00	00.00	00.00	00.00
2.	1	9.000	11.00	11.50	13.40

3.	2	14.53	16.63	17.54	20.10
4.	3	20.10	22.40	22.70	24.50
5.	4	24.81	26.81	27.50	28.40
6.	5	32.44	34.54	35.60	37.50
7.	6	40.21	44.31	44.80	45.31
8.	7	48.72	52.72	54.72	56.72
9.	8	56.45	60.45	61.10	63.25
10.	9	68.35	70.54	72.35	72.00
11.	10	73.80	76.70	77.80	79.40
12.	11	78.50	79.40	80.50	82.90
13.	12	80.50	82.50	84.60	86.10

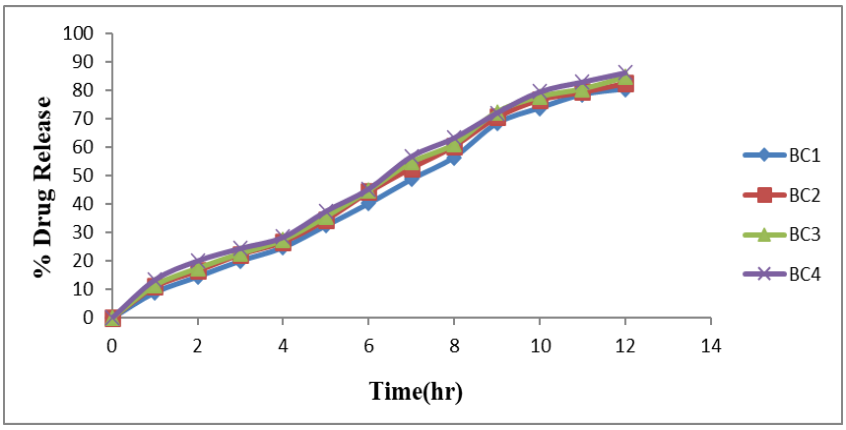


Figure 13: Comparative in-vitro drug release profile of formulations BC1, BC2, BC3 and BC4 in SGF (pH-1.2).

Table 10: Comparative in-vitro drug release profile of formulations CC1, CC2, CC3 and CC4 in SGF (pH-1.2).

S. No.	Time(hr)	Comparative % drug release			
		CC1	CC2	CC3	CC4
1.	0	00.00	00.00	00.00	00.00
2.	1	9.500	8.260	6.590	4.300
3.	2	16.36	14.35	9.450	7.250
4.	3	21.50	19.26	15.30	12.25
5.	4	27.18	25.28	22.25	17.30
6.	5	37.25	35.10	33.00	25.33
7.	6	45.66	43.60	40.50	35.00
8.	7	55.50	53.50	48.35	46.45
9.	8	66.45	64.45	60.00	58.00
10.	9	72.86	70.45	67.96	64.84
11.	10	76.40	74.00	70.56	68.46
12.	11	80.00	76.00	75.89	73.82
13.	12	84.50	81.50	79.00	77.45

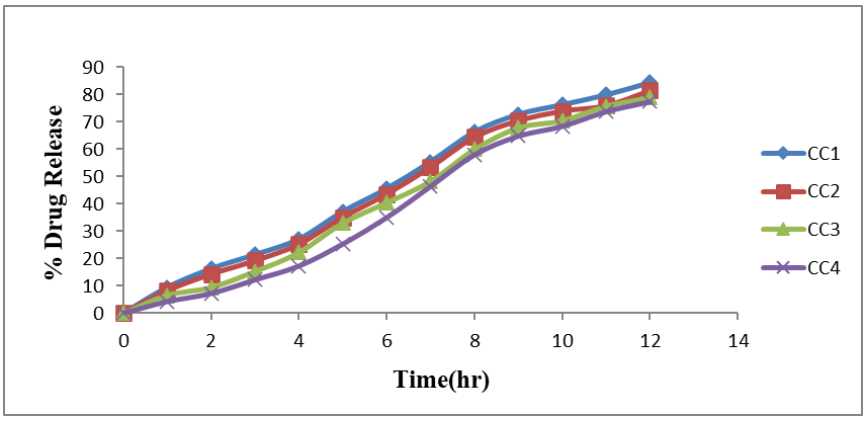


Figure 14: Comparative in-vitro drug release profile of formulations CC1, CC2, CC3 and CC4 in SGF (pH-1.2).

For the development of hydrogels formulations, the prepared formulations batches and development of formulations, by varing the concentration of polymer and crosslinker, then optimization of formulations, basis on the % release profile, the selected formulations of best release in the different batches.

The pH sensitive swelling behavior of hydrogels formulations carried out in both acid and basic medium, and then increase the pH medium 2.0 to 8.0, the swelling behavior was decrease.

Temperature sensitive swelling behavior was also carried out at 37°C and 20°C, which shows a typical positive swelling change with temperature. Maximum swelling was observed at 37°C and minimum swelling at 20°C.

The in-vitro release profile of famotidine was carried out in simulated gastric fluid (pH-1.2). The result indicates that the formulation AC1 to AC4, BC1 to BC4 and CC1 to CC4 show the % drug release. The release of drug significantly increased with decreasing crosslinking agent concentration and increasing polymer concentration. The drug release will ensure maximum availability of the drug in the stomach thereby maintaining peptic ulcer in the stomach.

References

[1]. Aminabhavi T.M., and Agnihotri S.A., (2006) Novel interpenetrating network chitosan-poly (ethylene oxide-g-acrylamide) hydrogel microspheres for the controlled release of capecitabine. Int. J. Pharm. 324: 103-115.

[2]. Abraham T.E., and George M., (2007) pH sensitive alginate-guar gum hydrogel for the controlled delivery of protein drugs. Int. J. Pharm. 335: 123-129.

[3]. Aikawa K., and Matsumoto K., (1998) Hydrogel formation of the pH response polymer poly-vinylacetal diethylaminoacetate. Int. J. Pharm. 167: 97-104.

[4]. Bajpai S.K., and Sonkusley J., (2002) Hydrogel for colon-specific oral drug delivery. Iranian. J. Polymer. 11: 187-196.

[5]. Brazel C.S., and Wu L., (2008) Surface cross linking for delayed release of proxyphylline from PHEMA hydrogels. Int. J. Pharm. 349: 1-10.

[6]. Brazel C.S., and Huang X., (2002) Minimization of initial burst in poly (vinyl alcohol) hydrogels by surface extraction and surface-preferential crosslinking. Int. J. Pharm. 248: 183-192.

[7]. Basit A.W., and Ibekwe V.C., (2006) A comparative in vitro assessment of the drug release performance of pH-responsive polymers for ileo-colonic delivery. Int. J. Pharm. 308: 52-60.

[8]. Bae Y.H., and Okano T., (1991) On-off thermocontrol of solute transport. Part 2. Solute release from thermosensitive hydrogels. Pharm. Res. 8: 624-628.

[9]. Cron W.C., Johnson B., and Niedermaier D.J., (2002) Mechanical properties of a pH sensitive hydrogel. Society for Experimental Mechanics.

[10]. Chen D., Qiao M., and Ma X., (2005) Injectable biodegradable temperature-responsive PLGA-PEG-PLGA copolymers: synthesis and effect of copolymer composition on the drug release from the copolymer-based hydrogels. Int. J. Pharm. 294: 103-112.

[11]. Davis, S.S., Hardy, J.G., Taylor, M.J., Whaley. D.R. and Wilson, C.J., Int. J. Pharm., 1984; 21: 331.

[12]. Vincent, H.K. Lee. And Joseph, R.R., Controlled Drug Delivery; Second Edition, Marcel Dekkerlnc., New York, 1987; 12.

[13]. Murray Weiner, Shepard Shapiro, Julius Axelrod, Jack R. Cooper and Bernard B. Brodie, Journal of Pharmacology and experimental Therapeutics, August 1950; 99 (4): 409-420 8.Ruth Mitchell Levine, Murray R. Blair and Byron B. Clark, Journal of Pharmacology and experimental Therapeutics, May 1955; 114 (1): 78-86 9.Weinatein, L., Antibiotics. In: Goodman, L.S. and Gilman.A. The pharmacological Basis of therapeutics. 4th Ed., Macmilan, New York; 1269, 1970.

[14]. Hoogerwerf, W.A., Pasricha, P.J., Goodman and Gilman's, The Pharmacological Basis of Therapeutics, XI Edition, Me Graw Hill Medical Publishing Division, 971-73.

[15]. http:// en. Wikipedia.org/wiki/peptic ulcer.

[16]. Hirotsu S., and Hirokawa Y., (1987) Volume-phase transition of ionized N-isopropylacrylamide gels. J. Chem. Phys. 87: 1392-1395.

[17]. Ichikawa H., and Fukumori Y., (2000) Novel positively thermosensitive controlled-release microcapsule with membrane of nanosized poly(N-isopropylacrylamide) gel dispersed in ethylcellulose matrix. J. Controlled Release. 63: 107-119.