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Formulation and *in vitro* evaluation of sustained release matrix tablets of roxatidine acetate HCl by using natural and synthetic polymers

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ABSTRACT

The work focuses mainly on sustaining the release of Roxatidine acetate Hcl, formulating them in to matrix tablets by using various matrix materials like Aloe barbadensis miller mucilage, HPMC K100 and Eudragit RSPO. Plasma half–life of Roxatidine acetate Hcl after oral administration, about 5 to 6 hrs and its bioavailability is 80%, So Roxatidine acetate Hcl is suitable for sustained drug delivery system, which may improve bioavailability. The granules were evaluated for angle of repose, loose bulk density, tapped bulk density and compressibility index. The tablets were subjected to various tests for physical parameters such as thickness, hardness, friability, drug content, and in vitro release studies. The prepared tablets were found to have better pharmacopoeial standard values. The drug release data fit well to the zero order. Korsmeyer's plot indicated that the drug release mechanism from the matrix tablet followed was Anomalous (non-Fickian) diffusion.

Keywords: Roxatidine acetate Hcl, *Aloe barbadensis* miller mucilage, HPMC K100, Eudragit RSPO, Wet granulation.

INTRODUCTION

Oral ingestion has been the most convenient and commonly employed route of drug delivery. Indeed, for sustained-release systems, the oral route of administration has by far received the most attention with respect to research on physiological and drug constraints as well as design and testing of products. This is because there is more flexibility in dosage form design for the oral route than there is for the parenteral route. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is well absorbed as the food stuffs that are ingested daily. In fact, the development of pharmaceutical product for oral delivery, irrespective of its physical form involves varying extent of optimization of dosage form characteristics within the inherent constraints of GI physiology. Therefore the fundamental understanding of various disciplines, including GI physiology, pharmacokinetics, pharmacodynamics and formulation design are essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form. The more sophisticated a delivery system, the greater is the complexity of these various disciplines involved in the design and optimization of the system. In any case, the scientific framework required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects[1]:

1. Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug.
2. The anatomic and the physiologic characteristics of the GIT.
3. Physicochemical characteristics and drug delivery mode of the dosage form to be designed.

Over the past two decades, sustained release dosage forms have made significant progress in terms of clinical efficacy and patient compliance as conventional formulations are required to be administered in multiple doses for the treatment of chronic conditions and therefore have several disadvantages. Matrix tablets composed of drug and polymer as release retardant offer the simplest approach in designing a sustained release system.[2]

Peptic ulcer disease is a term sometimes used for stomach ulcers. Ulcers from peptic ulcer disease can also affect the small intestine, called duodenal ulcers. The symptoms are gnawing or burning pain in the middle or upper stomach between meals or at night, Bloating, Heartburn, Nausea or vomiting, Severe pain in the mid- to upper abdomen. And these are caused by *H pylori* bacterium, taking NSAIDs such as aspirin, ibuprofen or naproxen, drinking alcohol regularly and smoking.[3]

Roxatidine acetate Hcl is used as an antiulcer drug, however, constipation remains one-off its side effect.[4] Roxatidine acetate Hcl is competitive inhibitor of histamine at the parietal cell H_2 receptor. It suppresses the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid. It accomplish this by two mechanisms: histamine released by ECL cells in the stomach is blocked from binding on parietal cell H_2 receptors which stimulate acid secretion and other substances that promote acid secretion (such as gastrin and acetylcholine) have a reduced effect on parietal cells when the H_2 receptors are blocked, so heal the ulcers caused by *H pylori* bacteria. Basal gastric acid output is reduced by more than 90%, 3 hours after administration of a single oral dose of roxatidine acetate 50mg to healthy volunteers or patients with peptic ulcer disease. Roxatidine acetate markedly reduces total pepsin output, but has no significant influence on serum pepsinogen I and gastrin levels in patients with peptic ulcer disease.[5]

The botanical name of Aloe vera is *Aloe barbadensis* miller. It belongs to Asphodelaceae (Liliaceae) family, and is a shrubby or arborescent, perennial, xerophytic, succulent, pea- green color plant. Aloe vera contains 75 potentially active constituents: vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids and amino acids.[6] Aloe barbadensis miller mucilage uses in the pharmaceutical preparations as Gelling agent and sustained release agent,[7] also It is most effective in the ulcer healing by (increasing the collagen content of the wound and also changed collagen composition and increased the degree of collagen cross linking)[8] and in constipation problem by increasing intestinal water content, stimulates mucus secretion and increases intestinal peristalsis)[9].

Hydrophilic polymer matrix systems are widely used for designing oral sustained drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance.[10] The hydrophilic polymers selected for the present study were Aloe barbadensis miller mucilage, Eudragit RSPO, HPMC K100. These polymers provide pH-independent drug release to oral dosage forms that can be used for formulating the sustained-release dosage forms.[11, 12]

MATERIALS AND METHODS

Materials: Roxatidine acetate Hcl was purchased from Leo chemicals, Bangalore. *Aloe barbadensis* leaves collected from Belagumba surrounding area, Tumkur, Karnataka. Eudragit RSPO was purchased from yarrow chemicals, Mumbai. Microcrystalline cellulose was purchased from Research- Lab Fine Chem Industries, Mumbai. Magnesium stearate, talc and PVP were purchased from SD Fine chemicals Ltd, Mumbai.

Extraction of *aloe barbadensis* miller mucilage[13]

The fresh *Aloe barbadensis* miller leaves were collected and washed with water. Incisions were made on the leaves and left over night. The leaves were crushed and soaked in water for 5–6 hrs, boiled for 30 minutes and left to stand for 1 hr to allow complete release of the mucilage into the water. The mucilage was extracted using a multi-layer muslin cloth bag to remove the marc from the solution. Acetone (three times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 40°C, collected, grounded, passed through a # 80 sieve and stored in desiccator at 30°C & 45% relative humidity till use.

Table 1: Chemical tests for *aloe barbadensis* miller mucilage

S. No	Phytochemical tests	Observations
1	Test for Alkaloids (Wagner's test)	+ve
2	Test for Carbohydrates (Molish's test)	+ve
3	Test for Proteins	+ve
4	Test for Tannins (Ferric chloride test)	-ve

Preparation of matrix tablets:

The matrix tablet was prepared from granules by conventional wet granulation method. A non-aqueous granulation process was adopted to prepare Roxatidine acetate Hcl matrix tablets. The drug and all other ingredients were sifted through sieve # 60. Then the sifted ingredients were mixed thoroughly in a mortar with pestle for 15min. IPA with PVP was added into well mixed powder till the desired wet mass was formed. This wet mass was sifted through sieve # 16 then granules are prepared. The prepared granules were dried at 60ºC for 1 hour in hot air oven, and then it was sifted through sieve # 16 and transferred the granules into a polybag. For lubrication add the magnesium

stearate and talc were sifted through sieve #40 and mixed with the prepared granules in a polybag for 5min. Finally tablets were compressed at 300 mg weight on a 10 station mini rotary tableting machine (Shakti Pharmatech Pvt. Ltd, Ahmedabad).

Evaluation of granules:
The angle of repose was measured by using funnel method which indicates the flow ability of the granules.[14] Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula: LBD= weight of the powder /volume of the packing.[15] TBD= weight of the powder /tapped volume of the packing. Compressibility index of the granules was determined by using the formula: CI (%) = [(TBD-LBD/TBD)] ×100.[16] The physical properties of granules were shown in Table 2.

Evaluation of tablets:
All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods [17] shown in Table 3.

Uniformity of drug content:
Accurately weighed quantity of the powder tablet equivalent to 100 mg of the drug was transferred to 100 ml volumetric flask. 50 ml of pH-1.2 buffer solution was added. Mix with the aid of ultrasound for 10 min, and then the volume was made up to 100 ml with the same buffer solution, mixed solution was filtered through the membrane filter disc with an average pore diameter not greater than 0.45µm. 5 ml of the filtrate was diluted to 100 ml with same buffer solution and examined under UV Spectrophotometer at 279 nm.

Drug release kinetics
Various mathematical equations have been proposed for kinetic analysis of drug release from the evaluated formulations. The zero order rate Eq. 1 describes the systems where the drug release is independent of its concentration. The first order rate Eq. 2 describes drug release from systems where the release is concentration dependent. According to the Higuchi model Eq. 3, drug release from the insoluble matrix is directly proportional to the square root of time and is based on Fickian diffusion: [18]

$Qt = k0\ t$ ……. *(1)*
$ln\ Qt = ln\ Q0 - k1t$ ……. *(2)*
$Qt = kH\ t1/2$ ……. *(3)*

where Qt is the amount of drug released at time t, $Q0$ is the initial amount of drug in the tablet and $k0$, $k1$ and kH are release rate constants for the zero order, first order and Higuchi models, respectively. In order to define a model that will represent a better fit for the formulations, dissolution data can be further analyzed by the Peppa's and Korsemayer's equation:

$Mt / M¥ = Kp\ tn$ ……. *(4)*

Where, Mt corresponds to the amount of drug released at time t, $M¥$ is the total amount of drug that must be released at infinite time, Kp is a constant and n is the release exponent indicating the type of drug release mechanism. The value of n for a cylinder is < 0.45, for Fickian release > 45 and < 0.8 for non-Fickian release, 0.89 for the case II release and > 0.89 for the super case II type release.[19] Criteria for selecting the most appropriate model were based on the best goodness of fit and smallest sum of squared residuals.

Table 2 : Composition of Roxatidine acetate Hcl sustained release matrix tablets prepared with different releases retardant natural matrices (in mg) (F-1 to F-9)

FORMULATION CODE	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	50	50	50	50	50	50	50	50	50
Eudragit RSPO	40	80	120	-	-	-	-	-	-
HPMC K100	-	-	-	40	80	120	-	-	-
Aloe barbadensis miller mucilage	-	-	-	-	-	-	40	80	120
PVP K30	15	15	15	15	15	15	15	15	15
MCC	186	146	106	186	146	106	186	146	106
Magnesium sterate	6	6	6	6	6	6	6	6	6
Talc	3	3	3	3	3	3	3	3	3

Table 3 : Granular properties of formulations F1 to F9 of Roxatidine acetate Hcl

Formulation No	Angle of repose	Loose bulk density (LBD)(g/ml)	Tapped bulk density(TBD)(g/ml)	Compressibility index (%)
F1	25.22 ±1.78	0.283 ±0.005	0.269 ±0.018	10.74 ±1.53
F2	26.23 ±1.84	0.264 ±0.007	0.275 ±0.017	9.65 ±1.66
F3	24.61 ±1.31	0.280 ±0.008	0.266 ±0.012	9.92 ±1.54
F4	27.41 ±1.51	0.261 ±0.008	0.275 ±0.011	10.94 ±1.74
F5	29.02 ±1.34	0.251 ±0.006	0.251 ±0.019	8.52 ±0.85
F6	28.12 ±1.21	0.282 ±0.003	0.285 ±0.017	11.62 ±1.23
F7	27.42 ±1.87	0.242 ±0.003	0.298 ±0.011	10.73 ±1.13
F8	28.54 ±1.29	0.254 ±0.007	0.253 ±0.014	11.20 ±1.42
F9	28.12 ±1.57	0.274 ±0.004	0.264 ±0.015	9.56 ±0.68

Table 4 : Tablets properties of formulations F1 to F9 of Roxatidine acetate Hcl

Formulation No	Thickness(mm)	Hardness(kg/cm^2)	Friability (%)	Drug content (%)
F1	3.65 ±0.09	7.3 ±0.25	0.33 ±0.35	99.21 ±0.16
F2	3.56 ±0.16	7.2 ±0.12	0.35 ±0.31	99.98 ±0.21
F3	3.46 ±0.12	7.1 ±0.33	0.31 ±0.21	98.99 ±0.14
F4	3.69 ±0.18	7.4 ±0.17	0.31 ±0.41	99.03 ±0.12
F5	3.70 ±0.12	7.2 ±0.18	0.35 ±0.21	99.02 ±0.16
F6	3.66 ±0.12	7.4 ±0.12	0.28 ±0.15	98.35 ±0.17
F7	3.77 ±0.12	7.8 ±0.15	0.32 ±0.43	99.30 ±0.12
F8	3.81 ±0.04	7.7 ±0.11	0.28 ±0.11	99.83 ±0.14
F9	3.71 ±0.14	7.5 ±0.10	0.29 ±0.11	99.84 ±0.13

Table 5 : Correlation coefficients of different mathematical models for formulations F-1toF-9

Formulation Code	Zero Order R^2	First Order R^2	Higuchi R^2	Peppa's- model	
				R^2	Slope n
F1	0.993	0.790	0.956	0.974	0.796
F2	0.992	0.547	0.946	0.954	0.864
F3	0.982	0.803	0.932	0.941	0.912
F4	0.992	0.769	0.952	0.971	0.798
F5	0.987	0.957	0.976	0.981	0.805
F6	0.997	0.937	0.965	0.989	0.861
F7	0.990	0.798	0.986	0.990	0.846
F8	0.985	0.701	0.989	0.990	0.898
F9	0.991	0.770	0.984	0.993	0.893

Stability Study:

The optimized formulation was subjected to stability at 25^{o}C± 2^{0}C / 60% ± 5% RH, 30^{0}C ± 2^{0}C / 65% ±5% RH and 40^{0}C ± 2^{0}C / 75% ± 5% RH for period of 90 days. After each month tablet sample was analyzed for physical characteristics and drug release profile.[20]

RESULTS AND DISCUSSION

Discussion on FT-IR:

FT-IR spectrum of Roxatidine acetate Hcl showed in Fig.1. FT-IR spectra of polymers like Eudragit RSPO, HPMC K100 and *Aloe barbadensis* miller are shown in Fig. (2 to 5). Drug polymer interaction was checked by comparing the IR spectra of the formulations with the IR spectra of the pure drug. There was no significant change in the functional groups between the IR spectrums of the pure drug and also no additional peaks were seen in the selected formulations. This supports that no interaction between drug and excipients. The characteristic peaks of the drug were observed in the spectra of mixture of drug and polymer mixture, however the intensity of the peaks were reduced this might be due to very low concentration of drug in the mixture this indicates that there is no interaction between the drug and polymer mixtures.

Characterization of granular properties

Granules prepared for compression of matrix tablets were evaluated for their flow properties, the results were shown in Tables 3. Angle of repose was in the range 24.61 ±1.31 to 29.02 ±1.34, which indicates excellent flow of the powder for all formulations. The bulk density of the powder formulation was in the range of 0.242 ±0.003 to 0.283±0.005 gm/cc, the tapped density was in the range of 0.251 ±0.019 to 0.298 ±0.011 gm/cc, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 8.52 ±0.85 to 11.62 ±1.23 indicating compressibility of the tablet blend is good. These values indicate that the prepared granules exhibited good flow properties.

Physicochemical evaluation of matrix tablets

1. Physical parameters (hardness & friability)

Tablets with a weight of 300 mg were subjected to quality control tests such as hardness, thickness and friability (Table 4). Hardness of the tablets was found to be in the range of 7.1 ±0.22 to 7.8 ±0.15 Kg/cm^2. It was within the range of monograph specification. Thicknesses of the tablets were found to be in the range of 3.46 ±0.12 to 3.95 ±0.08 mm. The friability of the tablets was found to be less than 1% and it was within the range of standard specification.

2. Weight variation and drug content

The average weights of the tablets were found to be within the prescribed official limits (IP). The drug content for all the batches was found to be in the range of 98.35 ± 0.17 to 99.98 ±0.21 (Table 4).

***In-Vitro* Release Study**

In-vitro release studies were carried out for all the formulations as per USP XXII tablet dissolution tester employing basket at 50 rpm using 900ml of 0.1 N Hcl for 2 hrs, after 2 hrs using 900ml pH 7.4 phosphate buffer as dissolution medium. The results were evaluated for 12 hrs. The temperature was maintained at 37 ±0.5^{0}C throughout the experiment. 5 ml of sample was withdrawn at predetermined time interval replacing with equal quantity of same buffered solution. The samples were filtered through 0.45µm membrane. Take 1ml filtrate in 10ml volumetric flask and volume made up to mark with same buffered solution. Drug content in each sample was analyzed after suitable dilution by UV/Visible spectroscopy at 279nm.

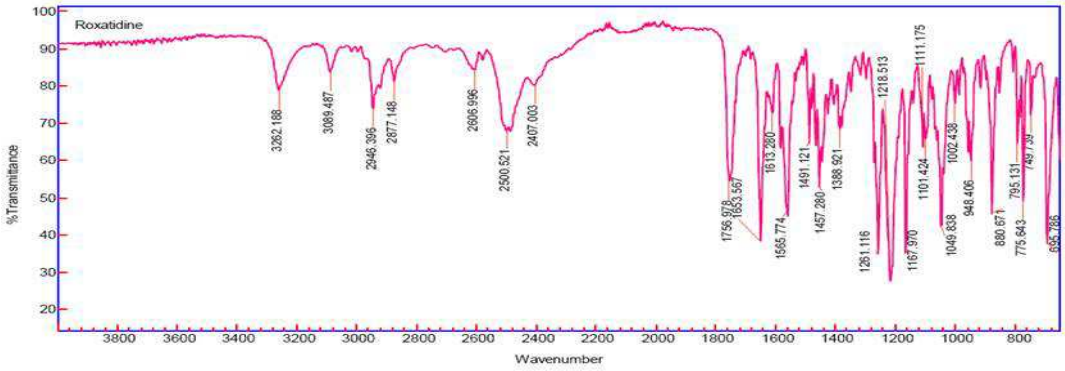

Figure 1 FT-IR spectroscopy of pure drug (Roxatidine acetate Hcl)

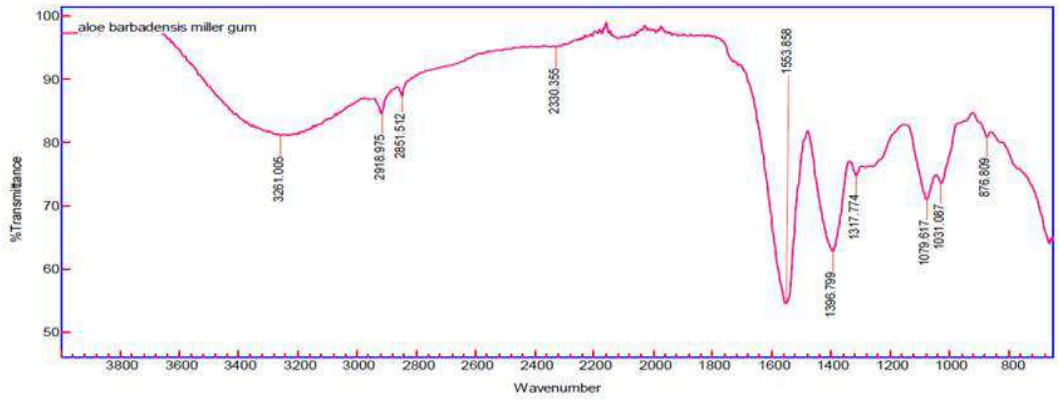

Figure 2 : FT-IR spectroscopy of *Aloe barbadensis* miller mucilage

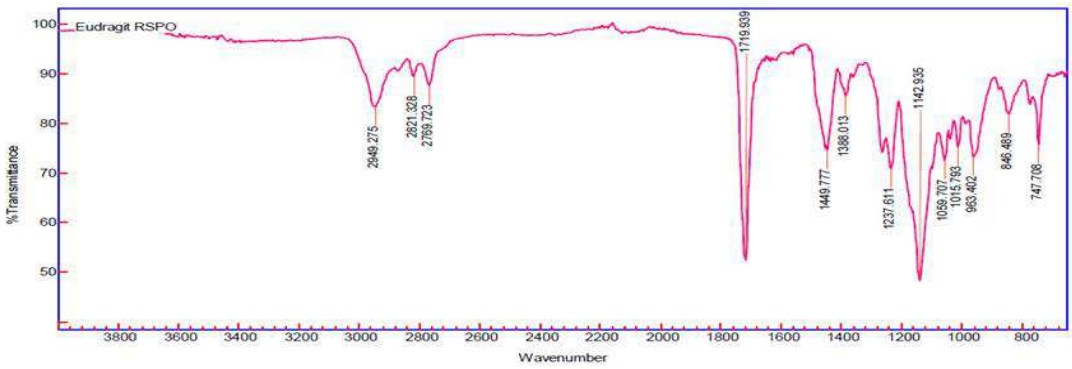

Figure 3 : FT-IR spectroscopy of Eudragit RSPO

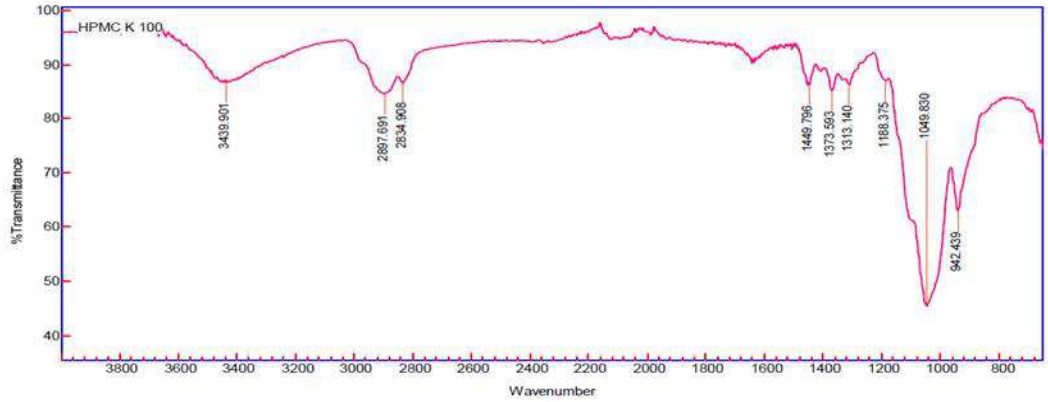

Figure 4 : FT-IR spectroscopy of HPMC K100

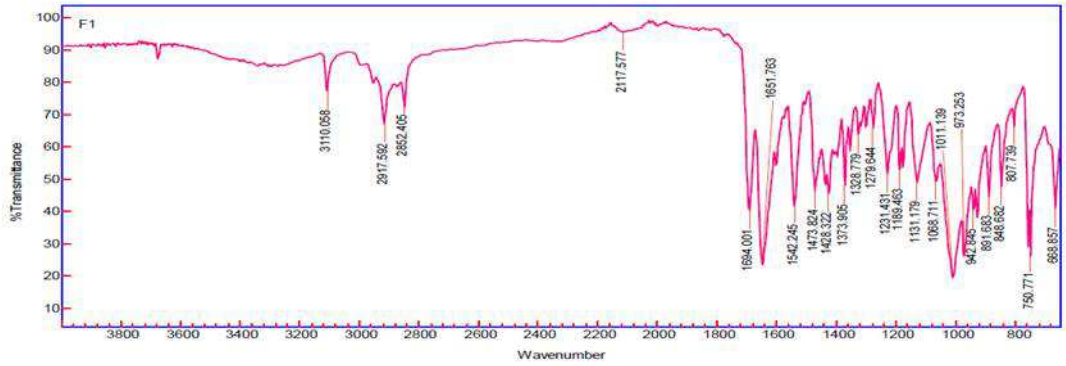

Figure 5 : FT-IR spectroscopy of formulation Eudragit RSPO.

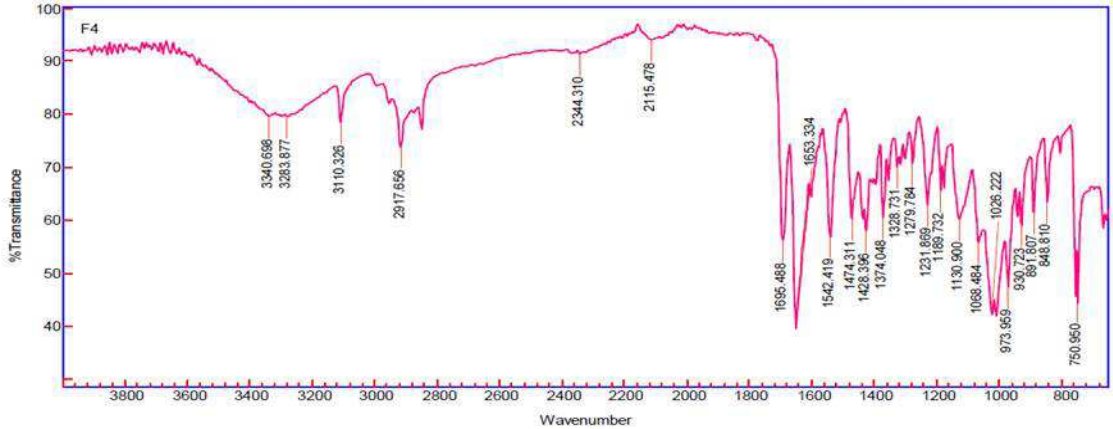

Figure 6 : FT-IR spectroscopy of formulation HPMC K100

The results of dissolution studies of these tablets indicates decrease in drug release from the formulation F-1 to F-3 by using eudragit RSPO which gave better controlled release for 12 hrs. Reason for the above could be because of low permeable nature of eudragit RSPO.

Incorporation of HPMC K100 in the formulations F-4 to F-6 showed better retarded the release rate of drug compared to eudragit RSPO formulation and drug release was decreased with increased polymer concentration. This might be due to quick hydration on the outer layer of tablet and gelatinous layer formation character of HPMC K100.

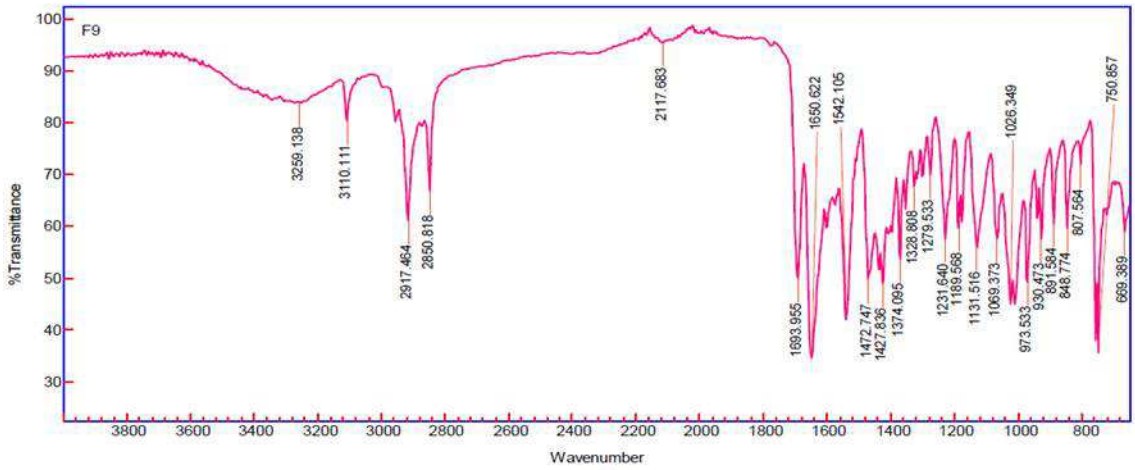

Figure 7 : FT-IR spectroscopy of Optimized formulation *Aloe barbadensis* miller mucilage

The present study revealed that the natural polymer *aloe barbadensis* miller mucilage powder formulation (F9) proved to be potential and economical sustained release retarding agent in the development of controlled release solid dosage forms. In the *aloe barbadensis* miller mucilage formulations (F7 to F9) observed that the *aloe barbadensis* miller mucilage powder concentration had a direct positive influence over the retarding characteristics of drug release from the tablet dosage form and also it's having greater pharmaceutical applications compared to the synthetic polymers. However it may act as synergizing action by anti-ulcerogenic effect and also overcome the side effects of entitled drug. *Aloe barbadensis* miller mucilage shows superior sustained release action at all concentration compared to the synthetic polymers HPMC K100 and Eudragit RSPO.

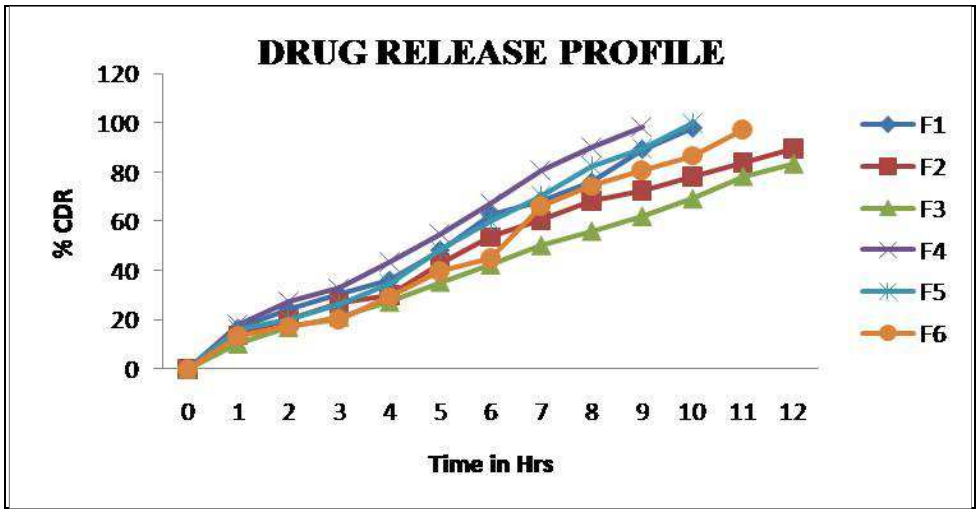

Figure 8 : Drug release profile

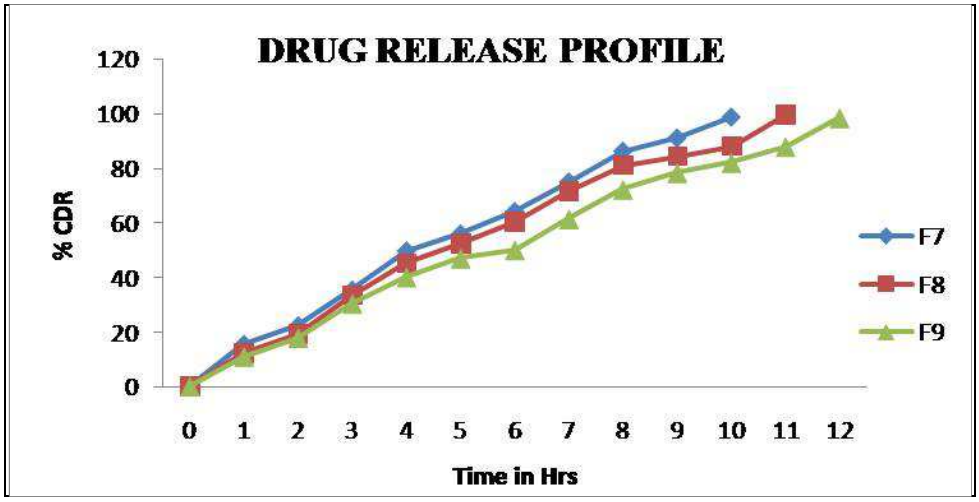

Figure 9 : Drug release profile

Determination of the release kinetics

The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of all formulations F-1 to F-9 could be best expressed by zero order equation as the plots showed highest linearity (R^2:0.982 to 0.997), than first order release kinetics (R^2: 0.547 to 0.957). The n values obtained from Korsmeyer Peppa's plots range from (0.796 to 0.912) indicate that mechanism of release of formulations F-1 to F-9 was Anomalous (non-Fickian) diffusion.

CONCLUSION

The present study was carried out to evaluate the natural and synthetic polymers for its matrix forming ability due to formation of thick gel structure, so we concluded that aloe barbadensis miller mucilage and HPMC K100 formulated tablets were found to be effective in sustaining the drug release up to 12 hr. Drug release was found to be diffusion coupled with erosion. During this study, it was also found that drug: polymer concentration ratio influences the drug release behaviour. Stability studies revealed that there was no considerable change in drug content and dissolution profile of matrix tablets. FT-IR studies resulted that all peaks corresponding to different functional groups of pure drug were present in the drug-exipient mixture no interaction between the drug and excipients. It can be concluded that stable formulation could be developed by incorporating natural and synthetic polymer in a definite proportion, so that the sustained released profile is maintained for an extended period. Release model of sample was found to follow zero order kinetics with high linearity. Mechanism of release from samples was demonstrating that the mechanism controlling the drug release was Anomalous (non-Fickian) diffusion.

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