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FORMULATION DEVELOPMENT AND *IN VITRO* CHARACTERIZATION OF HYDROCHLORTHIAZIDE TABLETS FOR GASTRO RETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

In the present research work formulation of Hydrochlorthiazide Floating tablets by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various grades of HPMC and Guar gum. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using Guar gum were unable to produce desired drug release, they were unable to retard drug release up to 12 hours. The formulations prepared with HPMC K 15 M retarded the drug release up to 12 hours in the concentration of 60 mg (F6).The formulations prepared with HPMC K100M were also retarded the drug release for more than 12 hours. Hence, they were not considered. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release

INTRODUCTION:

The oral route is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and gets absorbed from these regions of the gastrointestinal tract (GIT) depending upon the physicochemical properties of the drug.

The rectal route has traditionally been used to administer medicaments in the form of suppositories and enemas to the distal gut, although such formulations rarely succeed in spreading beyond the descending colon. Also, the rectal route is not convenient or acceptable for most patients and hence the oral route is the preferred route of drug administration. However, colonic drug delivery via the oral route is not without its challenges. The colon

constitutes the most distal segment of the gastrointestinal tract and so an orally administered formulation must retard drug release in the upper gastrointestinal regions but release the drug promptly on entry into the colon.

Numerous drug entities based on oral delivery have been successfully commercialized, but many others are not readily available by oral administration, which are incompatible with the physical and/or chemical environments of the upper gastrointestinal tract (GIT) and/or demonstrate poor uptake in the upper GIT. Due to the lack of digestive enzymes, colon is considered as suitable site for the absorption of various +-drugs. Over the past two decades the major challenge for scientist is to target the drugs specifically to the colonic region of GIT. Previously colon was considered as an innocuous organ solely responsible for absorption of water, electrolytes and temporary storage of stools. But now it is accepted as important site for drug delivery.

Colon targeting is used to treat:

Seriousness from constipation and diarrhea to the debilitating inflammatory bowel diseases(Ulcerative colitis and Crohn's disease) through to colon carcinoma which is two third cause of cancer in both man and women. Colon can be utilized as portal for the entry of drugs into the blood stream for the systemic therapy. Colon having the lower level of luminal and mucosal digestive enzymes as compared with the small intestine reduces the chances of drug degradation. E.g.to facilitate absorption of acid and enzymatically labile materials especially proteins and peptides. Colon delivery also a mean of achieving chronotherapy of disease that is sensitive to circadian rhythm such as asthma and arthritis Targeted delivery ensures the direct treatment at the disease site, lower dosing, and reduction in side effects. Colonic drug delivery is also found useful for improving systemic absorption of drugs like nitr-endipine (calcium channel blocker), metoprolol (antihypertensive), iso-sorbide mononitrate (antianginal). The rectal route has traditionally been used to administer medicaments in the form of suppositories and enemas to the distal gut, although such formulations rarely succeed in spreading beyond the descending colon. Also, the rectal route is not convenient or acceptable for most patients and hence the oral route is the preferred route of drug administration. However, colonic drug delivery via the oral route is not without its challenges. The colon constitutes the most distal segment of the gastrointestinal tract and so an orally administered formulation must retard drug release in the upper gastrointestinal regions but release the drug promptly on entry into the colon. Retardation of drug release in the diverse and hostile conditions of the stomach and small intestine is not easily achieved, since the dosage form will be subjected to a physical and chemical assault that is designed to break down ingested materials. While in the colon, the low fluid environment and viscous nature of luminal contents may hinder the dissolution and release of the drug from the formulation. Moreover, the resident colonic microflora may impact on the stability of the released drug via metabolic degradation. In spite of these potential difficulties, a variety of approaches have been used and systems have been developed for the purpose of achieving colonic targeting. Targeted drug delivery is reliant on the identification and exploitation of a characteristic that is specific to the target organ. In the context of colonic targeting, the exploitable gastrointestinal features include pH, transit time, pressure, bacteria and prodrug approach.

Factors to be considered in the design of colon specific drug delivery system

To reach the colon and to be able to specifically deliver and absorb the drug there, the dosage forms must be formulated taking into account the obstacles of the gastrointestinal tract. The various strategies developed to achieve this goal have used the specific character istics of this organ, i.e. transit time, pH, microflora, enzymes disease and the colonic environment. Nevertheless, these parameters can vary from one individual to the next and also according to the pathological condition and diet documented that gastric emptying varies with different types of dosage forms.

Drugs Suitable For Colonic Drug Delivery

Drug delivery selectively to the colon through the oral route is becoming increasingly popular for the treatment of large intestinal diseases and for systemic absorption of protein and peptide drugs. There has been an increasing interest in utilizing the colon as a site for systemic absorption of these drugs in view of the less hostile

environment prevailing in the colon. A variety of protein and peptide drugs like calcitonin, interferon, interleukins, erythropoietin and even insulin are being investigated for their absorption using colon specific drug delivery. Inflammatory bowel disease (IBD) such as ulcerative colitis and Crohn's disease require selective local delivery of drugs to the colon. Sulfasalazine is the most commonly prescribed drug for such diseases. Selective delivery of the drug to the colon is required for therapeutic efficacy with less or no side effects. The other drugs used in IBD are steroids, such as dexamethasone, prednisolone, and hydrocortisone. In colonic cancer, anticancer drugs like 5-flurouracil, doxorubicin, and nimustine are to be delivered specifically to the colon. The site specific delivery of drugs like, metronidazole, mebendazole, albendazole is used in the treatment of infectious diseases, such as amoebiasis and helmenthiasis. Besides peptide and protein drugs, the colon is also a good site for the absorption of drugs that are not stable in the acidic environment of the stomach, cause gastric irritation (e.g. aspirin, iron supplements) or those degraded by small intestinal enzymes. A number of drugs available as sustained release or delayed release or timed release tablets or capsules for oral administration are anti-inflammatory drugs, anti-hypertensive drugs, etc. Unless these drugs have good absorption characteristics in the colon, their intended use in the management of respective disorder s through sustained release or timed release formulations will be in question. The drugs that are having good absorption properties from the colon include theophylline, glibenclamide and oxeprenolol. Diclofenac, ibuprofen, nitrenidipine, isosorbide, metoprolol (anti-hypertensive), nifedipine etc. and hence can be investigated for better bioavailability through colon specific drug delivery.

Approaches to colon-specific drug delivery

In recent years, a large number of solid formulations targeting the lower parts of the Gastro Intestinal Tract, especially the colon, have been reported. These formulations may be broadly divided into four types, which are:

1. pH- dependent system designed to release a drug in response to change in pH
2. Time controlled (or Time-dependent) system designed to release a drug after a predetermined time.
3. Microbially-controlled system making use of the abundant entero-bacteria in the colon.
4. Enzyme- based system. Prodrug.
5. Pressure-dependent system making use of luminal pressure of the colon.

Among these, first three are most widespread formulation technologies being developed for pharmaceutical market.

P^H-Dependent Systems:

Solid formulations for colonic delivery that are based on pH-dependent drug release mechanism are similar to conventional enteric-coated formulations but they differ in target site for delivery and therefore type of enteric polymers. In contrast to conventional enteric-coated formulations, colonic formulations are designed to deliver drugs to the distal (terminal) ileum and colon, and utilize enteric polymers that have relatively higher threshold pH for dissolution most commonly used polymers (Table 1) are derivatives of acrylic acid and cellulose. These polymers have ability to withstand an environment ranging from low pH (~1.2) to neutral pH (~7.5) for sever al hour s. Apparently, it is highly desirable for pH- dependent colonic formulations to maintain their physical and chemical integrity during passage through the stomach and small intestine and reach the large intestine where the coat should disintegrate to release the drug locally. It should be however noted that Gastro Intestinal fluids might pass through the coat while the dosage form transits through the small intestine. This could lead to premature drug release in the upper parts of Gastro Intestinal tract and as a result loss of therapeutic efficacy may occur. One approach to overcome this problem is to apply higher coating levels of enteric polymers; however, this also allows influx of Gastro Intestinal fluids through the coat, and the thicker coats often rupture under the influence of contractile activity in the stomach. In general, the amount of coating required depends upon the solubility characteristics (solubility, dose/solubility ratio) of the drug, desired release profile and surface area of the formulation, and composition of the coating solution/dispersion. Widely used polymers are methacrylic resins (Eudragit S), which are available in water soluble and water-insoluble forms. Eudragit L and S are copolymers of methacrylic acid and methyl

methacrylate. To overcome the problem of premature drug release, a copolymer of methacrylic acid, methyl methacrylate and ethyl acrylate (Eudragit FS), which dissolves at a slower rate and at a higher threshold pH (7–7.5), has been developed recently colon targeted drug delivery systems based on methacrylic resins has described for insulin, prednisolone, quinolones, salsalazine, cyclospore beclomethasone dipropionate, and naproxane, pH-sensitive delivery systems are commercially available for mesalazine, (5-aminosalicylic acid) and budesonide for the treatment of ulcerative colitis and Crohn's disease respectively.

Time-controlled (or time-dependent) systems:

Time-controlled systems are useful for synchronous delivery of a drug either at preselected times such that patient receives the drug when needed or at a pre-selected site of the GIT. These systems are therefore particularly useful in the therapy of diseases, which depend on circadian rhythms. Time-controlled formulations for colonic delivery are also delayed-release formulations in which the delay in delivery of the drug is time- based. In these systems, it has been suggested that colonic targeting can be achieved by incorporating a lag time into the formulation equivalent to the mouth to colon transit time.

Ideally, formulations are designed such that the site of delivery (i.e. colon) is not affected by the individual differences in the gastric emptying time, pH of the stomach and small intestine or presence of anaerobic bacteria in the colon. A nominal lag time of 5 hours is usually considered sufficient, since small intestinal transit has been considered relatively constant at 3 to 4 hours. In principle, time-controlled systems rely on this consistent small intestinal transit time. The drug release from these systems therefore occurs after a predetermined lag phase, which is precisely programmed by selecting a suitable combination of controlled-release mechanisms.

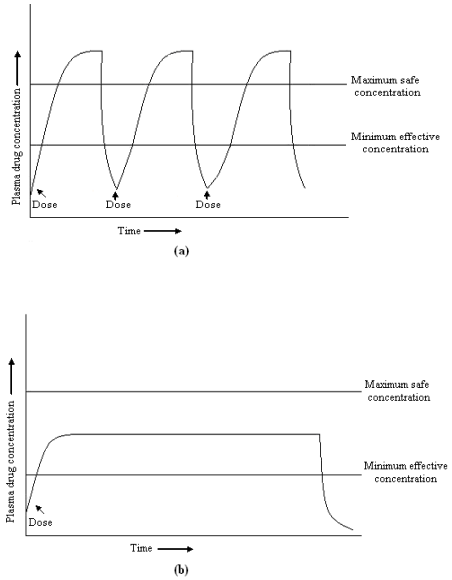

Figure 1 (a): Drug levels in the blood with traditional drug dosing (b) Drug levels in the blood with controlled-delivery dosing**.**

Available technologies based on the time controlled systems are:

1. **Codes system:** comprises a series of polymer s that are combined to protect the drug core until the formulation arrives in the colon.
2. **Colon-Targeted Delivery System -** uses lag time to achieve colon delivery. The system is comprised of three parts: an outer enteric coat, an inner semipermeable polymer membrane, and a central core comprising swelling excipients and an active component.
3. **Oros-CT:** is a technology developed by Alza Corporation and consists of an enteric coating, a semiper meable membrane, a layer to delay drug release, and a core consisting of two compartments.
4. **Time Clock - delivery device:** developed by Pozzi and colleagues is pulsed delivery system based on a coated solid dosage form.

METHODOLOGY

Analytical method development:

a) Determination of absorption maxima:

A solution of containing the concentration 10 µg/ ml was prepared in 0.1N HCl , 7.4 pH & phosphate buffer 6.8pH respectively, UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

b) Preparation calibration curve:

10mg of drug was accurately weighed and dissolved in 10ml of 0.1N HCl, 7.4 PH, and 6.8 PH in 10 ml volumetric flask, to make (1000 µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100 µg/ml) standard stock solution (2), then again 1 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 2, 4,6, 8, 10, 12, 14, 16, 18 ,and 20µg/ml with 0.1N HCl, 7.4 pH, and 6.8 pH. The absorbance of standard solution was determined using UV/ VIS spectrophotometer at 273nm. Linearity of standard curve was assessed from the square of correlation coefficient (r2) which determined by least-square linear regression analysis.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel.

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting.

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit.

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

Formulation development of Tablets:

Scopalamine colon targeted tablets were prepared by using compression coating technology. Initially internal core tablet containing drug and super disintegrate was formu-

lated. For the prepared core tablet compression coating is done by using various compositions of polymers. Ethyl cellulose, Polymethacrylate polymers such as Eudragit L100 and Eudragit S100 are used as polymers for compression coating.

Tablets are developed in two stages

1) Preparation of core tablet containing drug and super disintegrate.

2) Compression coating of prepared core tablets.

Formulation of core tablet:

The core tablets are formulated by using 20 mg of drug molecule, sodium starch glycollate as super disintegrate, Micro crystalline cellulose as diluent, talc and magnesium stearate as Glidant and Lubricant respectively. The composition of core tablet was given in table. Total weight of core tablet was fixed as 60 mg. The tablets are prepared by using 5mm flat punch. Then the prepared core tablets are subjected to compression coating by using various compositions of polymers.

Formulation of compression coated tablets:

The prepared core tablets were subjected to compression coating by using various compositions of polymers such as Ethyl cellulose, Eudragit L 100 and Eudragit S 100 as coating materials.the composition of coating layer is given in table.

Compression coating layer was divided into two equal portions i.e., 120mg of each quantity .Half of the quantity of powder blend was placed in the die cavity, core tablet was placed exactly in the middle of die cavity and then remaining quantity of powder blend was placed over the core tablet so that the powder blend should cover all the sides and top side of core tablet uniformly. Then the tablets are compressed by using 9mm flat surfaced punch using 8 station tablet punching machine with the hardness of 4-4.5 kg/cm^2.Then the prepared compression coted tablets are evaluated for various post compression parameters as per standard specifications.

Evaluation of post compression parameters for prepared Tablets

The designed formulation compression coated tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage.

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations).

Determination of drug content:

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Scopalamine were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

Drug release studies of Compression coated Scopalamine tablets:

The release of Scopalamine from coated tablets was carried out using USP paddle-type dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37±0.5 °C. For tablets, simulation of gastrointestinal transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in simulated gastric fluid (SGF, pH 1.2) for the first 2 hours as the average gastric emptying time is about 2 hours. Then, the dissolution medium was replaced with enzyme- free simulated intestinal fluid (SIF, pH 7.4) and tested for drug release for 3 hours, as the average small intestinal transit time is about 3 hours, and finally enzyme- free simulated intestinal fluid (SIF, pH 6.8) was used upto 12 hours to mimic colonic pH conditions.

Drug release was measured from compression coated Scopalamine tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples withdrawn at various time intervals were analyzed spectrophotometrically at 275 nm and 270 nm respectively. All dissolution runs were performed for six batch. The results were given with deviation.

Application of Release Rate Kinetics To Dissolution Data :

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

***In vitro* drug release studies**

Drug release studies of Scopalamine core tablets:

The core tablets containing 15mg Scopalamine of were tested in (pH 6.8), for their dissolution rates. Dissolution studies were performed using USP paddle type sample of 5 ml was withdrawn and replaced with equal volume of fresh medium. The samples were analyzed spectrophotometrically at respective 270 nm.

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$\text{Log } (100\text{-}F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\, t1/2$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t/ M_\infty = K\, t^n$$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the

diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

Hixson-Crowell release model:

$$(100\text{-}Q_t)^{1/3} = 100^{1/3} - K_{HC}.t$$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

RESULTS AND DISCUSSION

The present study was aimed to developing compression coated Scopalamine formulations for colon targeting using ethyl cellulose and enteric coating polymers like Eudragit L100 and Eudragit S 100. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

Analytical Method

Graphs of Scopalamine was taken in Simulated Gastric fluid (pH 1.2) and Simulated Intestinal Fluid (pH 6.8 and 7.4)

Scopalamine blend was subjected to various pre-formulation parameters. The apparent bulk density and tapped bulk density values ranged from 0.52 to 0.581 and 0.606 to 0.671 respectively. According to Tables 7.4, the results of angle of repose and compressibility index (%) ranged from 32.74±0.12 to 37.08±0.96 and 13.37±0.38 to 14.72±0.62 respectively. The results of angle of repose (<35) and compressibility index (<23) indicates fair to passable flow properties of the powder mixture. These results show that the powder mixture has good flow properties. The formulation blend was directly compressed to tablets and *in-vitro* drug release studies were performed.

Quality Control Parameters For compression coted tablets: Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet. Total weight of tablet including core is 300 mg. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

In-Vitro Drug Release Studies

The compression coated tablets containing 15mg of Scopalamine were tested in 6.8 pH phosphate buffer solution for their dissolution rates. The release of Scopalamine from compression coated tablets was carried out using USP paddle-type dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37±0.5 °C. For tablets, simulation of gastrointestinal transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in simulated gastric fluid (SGF, pH 1.2) for the first 2 hours as the average gastric emptying time is about 2 hours. Then, the dissolution medium was replaced with enzyme- free simulated intestinal fluid (SIF, pH 7.4) and tested for drug release for 3 hours, as the average small intestinal transit time is about 3 hours, and finally enzyme- free simulated intestinal fluid (SIF, pH 6.8) was used upto 12 hours to mimic colonic pH conditions. Drug release was measured from compression coated Scopalamine tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples withdrawn at various time intervals were analyzed spectrophotometrically at 275 nm ,319 and 320 nm respectively. All dissolution runs were performed for six batches. From the dissolution values it was evident that the formulations F3 & F9 were retarded the drug release up to 12 hours, they shown drug release of 98.69 and 96.45 % respectively. Formulations F1 –F3 contains ethyl cellulose alone. As the concentration of ethyl cellulose increases retardation nature was increased.F3 formulation containing 150 mg of ethyl cellulose was show almost negligible amount of drug release in first 3 hours from the 5 th hour onwards it shown drug release as the time proceeds slowly the polymer was undergone erosion and allowed the drug to come out from the dosage form. The formulation was retarded drug release up to 12 hours and it showed maximum drug release in 12 hours i,e., in colon region. Similarly the formulation F9 containing Eudragit L 100 in the concentration of 150 mg also showed similar drug release pattern.

Table 1: Optimization sodium bicarbonate concentration

S.No	Composition	EF1	EF2	EF3
1	Hydrochlorthiazide	12.5	12.5	12.5
2	HPMC K 100M	20	40	60
4	$NaHCO_3$	20	20	20
5	Mg.Stearate	3	3	5
6	Talc	3	3	3
7	MCC pH 102	Q.S	Q.S	Q.S

All the quantities were in mg.

Table 2: Formulation composition for floating tablets

Formulation code	Hydro-chlorthiazide	Guar gum	HPMC K15M	HPMC K100M	$NaHCO_3$	Mag. Stearate	Talc	MCC pH
F1	12.5	20	-----	-----	20	3	3	QS
F2	12.5	40	-----	-----	20	3	3	QS
F3	12.5	60	-----	-----	20	3	3	QS
F4	12.5	-----	20	-----	20	3	3	QS
F5	12.5	-----	40	-----	20	3	3	QS
F6	12.5	-----	60	-----	20	3	3	QS
F7	12.5	-----	-----	20	20	3	3	QS
F8	12.5	-----	-----	40	20	3	3	QS
F9	12.5	-----	-----	60	20	3	3	QS

All the quantities were in mg, total weight is 200 mg.

Table 3: Pre formulation parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's in-dex (%)	Hausner's Ratio
F1	26.01	0.49±0.07	0.57±0.01	16.21±0.06	0.86±0.06
F2	24.8	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05
F3	22.74	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
F4	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F5	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	26.12	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F7	27.08	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F8	25.12	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F9	25.45	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02

Table 4: Quality Control Parameters For tablets

Formulation codes	Weight varia-tion(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug con-tent (%)	Flaoting lag time (min)
F1	212.5	4.5	0.52	3.8	99.76	4.0
F2	205.4	4.2	0.54	3.9	99.45	4.2
F3	198.6	4.4	0.51	3.9	99.34	4.5
F4	210.6	4.5	0.55	3.9	99.87	4.1
F5	209.4	4.4	0.56	3.7	99.14	4.0
F6	210.7	4.2	0.45	3.5	98.56	4.4
F7	202.3	4.1	0.51	3.4	98.42	4.5
F8	201.2	4.3	0.49	3.7	99.65	4.6
F9	298.3	4.5	0.55	3.6	99.12	4.7

Table 5: Dissolution Data of Hydrochlorthiazide Tablets Prepared With Guar gum In Different Concentrations

Time (hr)	Cumulative percent drug dissolved (n=3±SD)		
	F1	F2	F3
0.5	21.73	18.52	19.53
1	59.23	37.47	28.97
2	84.9	59.93	35.89
3	94.873	65.85	45.7
4	94.873	77.54	54.38
5	--	89.55	61.2
6	--	96.6	67.06
7	--	--	72.52
8	--	--	77.88
9	--	--	86.6
10	--	--	89.09
11	--	--	94.52

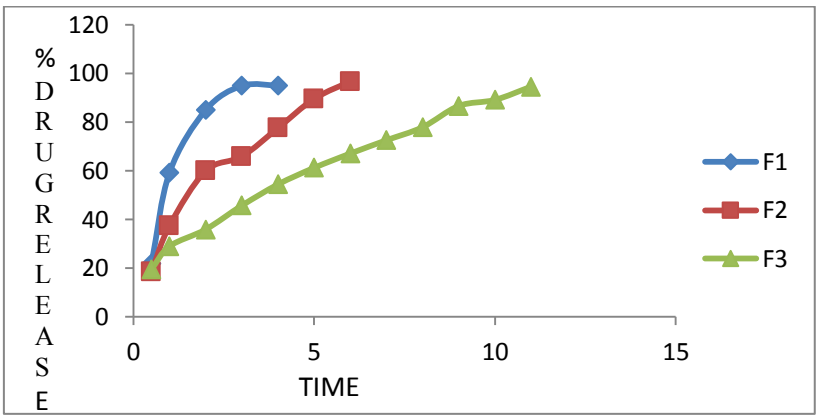

Fig 2: Dissolution profile of hydrochlorthiazide floating tablets (F1 to F3)

Table 6: Dissolution Data of hydrochlorothiazide Tablets Prepared With HPMCK15M In different concentrations

Time (hr)	cumulative percent drug dissolved (n=3±SD)		
	F4	F5	F6
0.5	18.45	18.42	19.62
1	36.26	27.73	27.86
2	52.16	35.63	36.35
3	70.01	42.04	41.45
4	87.26	57.25	47.80
5	93.10	64.33	55.25
6		75.41	60.24
7		83.84	66.73
8		92.80	71.34
9			78.52
10			80.17
11			88.75
12			96.33

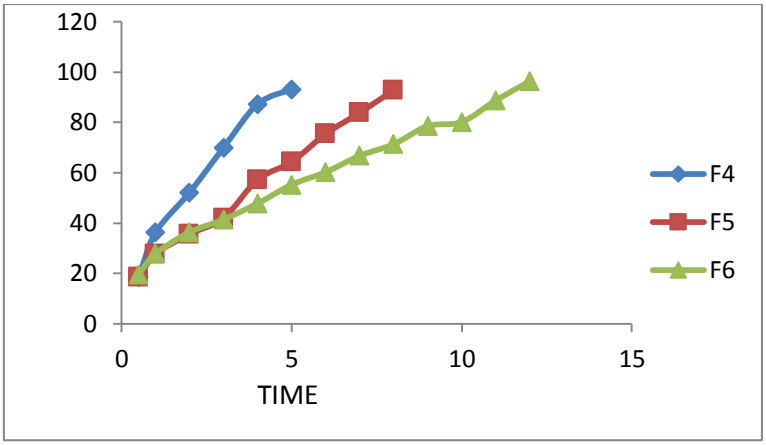

Fig3: Dissolution profile of Hydrochlorthiazide HCl floating tablets (F4, F5, F6).

Table 7: Dissolution Data of Hydrochlorthiazide Tablets Prepared With HPMC K100M In Different Concentrations

Time (hr)	Cumulative percent drug dissolved (n=3±sd)		
	f7	f8	F9
0.5	18.81	19.89	14.21
1	29.02	28.04	18.87
2	35.70	35.43	27.19
3	43.32	41.65	35.66
4	49.25	47.18	43.32
5	55.28	53.81	51.06
6	60.92	58.89	57.13
7	66.08	64.53	63.63
8	70.44	69.43	69.71
9	77.22	72.83	73.34
10	80.90	79.98	79.27
11	87.83	83.52	82.86
12	91.90	88.65	85.97

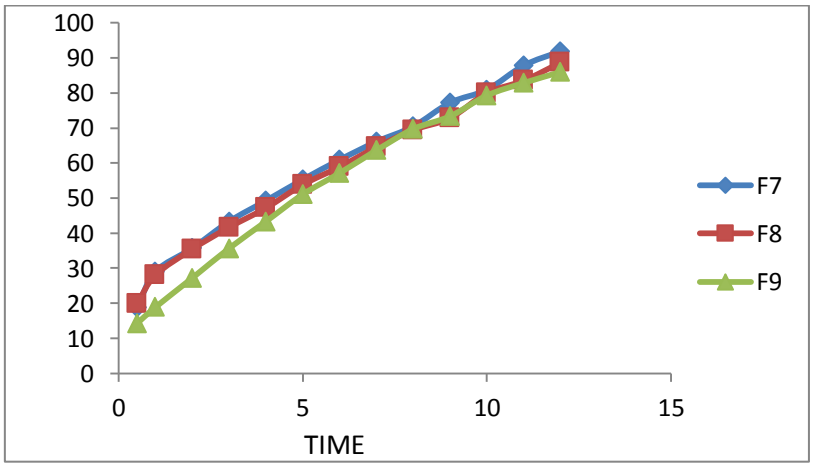

Fig 8: Dissolution profile of hydrochlorthiazide HCl floating tablets (F7, F8, F9)

CONCLUSION

In the present research work sustained release matrix formulation of Scopalamine targeted to colon by using various polymers developed. To achieve pH-independent drug release of Scopalamine , pH modifying agents (buffering agents) were used. Colon targeted tablets were prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethyl cellulose, Eudragit L100 and S100 were used as enteric coating polymers. The precompression blend of all formulations was subjected to various flow property tests and all the formulations were passed the tests. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques. The tablets were passed all the tests.Among all the formulations F3 formulation was found to be optimized as it was retarded the drug release up to 12 hours and showed maximum of 98.69% drug release. It followed zero order kinetics mechanism.

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