Irritable bowel syndrome (IBS) is a mild intestinal chronic disorder associated with abdominal pain, altered bowel motility resulting in either diarrhea or constipation, and increased visceral hypersensitivity and pain. IBS is one of the most common functional gastrointestinal disorders. It has an estimated prevalence of 8-22% in the general population.

Antispasmodic drug have traditionally formed the basis of treating irritable bowel syndrome. Dicyclomine, an anticholinergic drug, has direct smooth muscle relaxant action and in addition exerts antispasmodic action. Plasma half-life of dicyclomine is 4-6 h. Dicyclomine commonly used for the treatment of irritable bowel syndrome is associated with number of side effects including the most serious one i.e. heat stroke. To control the rise in body temperature, antipyretic drugs are generally administered concurrently. The most commonly used drug for this purpose is paracetamol. Paracetamol (PCM), an antipyretic and analgesic drug which has a short half life in plasma, about 1–4 hours. Paracetamol may reduce rise in body temperature and abdominal pain as well. However, Paracetamol is associated with many contraindicative manifestations including hypertension, allergic reaction and etc.

Conventional therapy of dicyclomine is not very effective for the treatment of IBS, as the drug molecules do not reach the target site in therapeutic concentration. Therefore effective treatment of IBS by conventional therapy requires relatively large dose to compensate for drug loss during passage through the upper gastrointestinal (GI) tract. These large doses may increase undue side effects associated with the drugs.

The present research work was aimed to overcome abovedited problem. Microsponges based colon specific drug delivery systems were expected to effectively target bioactive compounds and increase residence time as well.

Microsponges are biologically inert, nonirritating, nonmutagenic, nonallergic, nontoxic polymeric drug delivery systems, which have shown great potential in the delivery of drugs at desired site. Microsponges can also be described as porous microspheres, which are fabricated by using cross-linked polymers (mainly substituted acrylates or styrene-divinyl benzene).
This study encompassed preparation and evaluation of microsponges based colon specific tablet formulations. Initially, microsponges of dicyclomine and paracetamol were prepared by quasi-emulsion solvent diffusion method using eudragit RS 100 and eudragit S-100. The reason for preparing microsponge due to earlier reports, which suggested that drug carrier, systems less than 200 μm may efficiently be taken up by the macrophages present in colon tissue, thus exhibiting effective localized drug action at the desired site. A subsequent increase of residence time that may be postulated for microsponges as compared to existing drug delivery systems may allow dose reduction and enhance therapeutic effect. Another reason for preparing microsponges was their sponge like texture because of which they can easily be compressed to produce mechanically strong tablets.

Thereafter, the core tablets of microsponges were prepared by direct compression method which were compression coated with pectin:HPMC mixture. The reason for selecting pectin was its selectively biodegradation in the colon by colonic flora. HPMC increased the mechanical strength of the tablet coat and helped in maintaining its integrity during its sojourn in the gastro-intestinal tract.

The drugs dicyclomine and paracetamol, selected for present study were identified using different methods reported in the literature viz. melting point determination, determination of absorption maxima ($\lambda_{\text{max}}$), loss on drying, and FTIR spectroscopy.

The thermogram of differential scanning colorimetry showed sharp endothermic peaks of dicyclomine and paracetamol at 174.23 °C and 175.97 °C, respectively corresponding to the melting range of the drugs in crystalline form (dicyclomine- 172-174 °C and paracetamol- 174-176 °C). Absorption maxima ($\lambda_{\text{max}}$) of dicyclomine and paracetamol were noted to be at wavelength 420 nm and 249 nm, respectively corresponding to the values reported in literature (dicyclomine - 420 nm and paracetamol - 249 nm). The loss on drying for dicyclomine and paracetamol was observed to be 0.69% (limit NMT 1.0 %) and 0.23 % (limit NMT 0.5 %), respectively.

FTIR spectra of the dicyclomine exhibited characteristic C-N, C-O, C-H, C=O (ester) stretching bands at 1134.07 cm$^{-1}$, 1193.85 cm$^{-1}$, 2929.67 cm$^{-1}$, 1718.45 cm$^{-1}$,
respectively. FTIR spectra of paracetamol showed characteristic O-H, N-H, C=O (amide) stretching bands at 3326.98 cm\(^{-1}\), 3413.77 cm\(^{-1}\), 1654.81 cm\(^{-1}\), respectively. Whereas, amide II band, C-N-H group and para-disubstituted aromatic rings were observed at 1560.30 cm\(^{-1}\), 1259.43 cm\(^{-1}\) and 837.05 cm\(^{-1}\), respectively. The FTIR spectra of both drugs confirmed their identity and purity.

Calibration curves of both the drugs were prepared in 0.1N HCl, phthalate buffer pH 4.5, phosphate buffer pH 6.8, phosphate buffer pH 7.4 and phosphate buffer pH 6.8 with pectinex ultra SPL. Calibration curve data of both the drugs were subjected to linear regression analysis. R-values were found to be 0.9995, 0.9997, 0.9998, 0.9998 & 0.9998 for dicyclomine and 0.9998, 0.9997, 0.9998 and 0.9998 for paracetamol in 0.1N HCl, phthalate buffer pH 4.5, phosphate buffer pH 6.8, phosphate buffer pH 7.4 and phosphate buffer pH 6.8 with pectinex ultra SPL, respectively indicating good linearity.

The solubility of both the drugs was determined in different media. Both drugs were found to be sparingly soluble in acidic medium and slightly soluble in basic medium. The solubility of dicyclomine in 0.1N HCl, phthalate buffer pH 4.5, phosphate buffer pH 6.8, phosphate buffer pH 7.4 was found to be 0.0163 gm/ml, 0.0083 gm/ml, 0.0069 gm/ml, and 0.0057 gm/ml, respectively. The solubility of paracetamol in 0.1N HCl, phthalate buffer pH 4.5, phosphate buffer pH 6.8, phosphate buffer pH 7.4 was found to be 0.0894 gm/ml, 0.0061 gm/ml, 0.0056 gm/ml, and 0.0049 gm/ml, respectively.

The compatibility of drugs with eudragit RS100, eudragit S100, and PVA was assessed by FTIR spectroscopy by keeping the samples at 40°C and 75% RH and at room temperature for 1 month. In FTIR spectra of paracetamol, characteristic N-H stretching band at 3413.77 cm\(^{-1}\), O-H stretching band at 3326.98 cm\(^{-1}\), and carbonyl stretching band at 1654.81 cm\(^{-1}\) were seen and in case of dicyclomine, characteristic C=O stretching band was observed at 1718.45 cm\(^{-1}\), which are in agreement with the reported values. Eudragit RS 100 showed an ester C=O stretching peak around 1726.17 cm\(^{-1}\) and eudragit S 100 showed carbonyl stretching at 1718.46 cm\(^{-1}\) & bond characteristic to carboxylic group in the range 2437-3473 cm\(^{-1}\) as reported in the literature. The results showed that no chemical interaction or changes took place in
the mixtures of the drugs and various excipients alone or in combination, as exhibited by the FTIR spectra, thus indicating compatibility of the drugs with all excipients.

Quasi-emulsion solvent diffusion method was used for preparation of microsponges. The drug and polymer in the ratios 3:1, 6:1, 9:1, 12:1 were taken to prepare different microsponge formulations. In each formulation, the amounts of polymer (200 mg), dichloromethane (5 ml), PVA (0.5% w/v) were kept constant. The microsponge formulations were prepared using mechanical stirrer (Remi RQ1217-D) at a stirring rate of 500 rpm for eudragit RS-100 based microsponges and 1000 rpm for eudragit S-100 based microsponges for 8 hours. The various microsponge formulations namely FDRS1, FDRS2, FDRS3, FDRS4 & FPRS1, FPRS2, FPRS3, FPRS4 containing drug(s):eudragit RS-100 in the ratios 3:1, 6:1, 9:1, 12:1, respectively and FDS1, FDS2, FDS 3, FDS4 and FPS1, FPS2, FPS3, FPS4 containing drug(s): eudragit S-100 in the ratios 3:1, 6:1, 9:1, 12:1, respectively were prepared.

The effect of various variables like drug to polymer ratio, stirring rate, volume of internal phase, amount of emulsifying agent on the nature of microsponges was studied.

The morphology of the microsponges was studied by scanning electron microscopy (SEM). The microsponges were observed to be spherical and uniform with no drug crystals on the surface. It was noted that drug-polymer ratio has considerable effect on the morphology and size of microsponges. It was observed that as the ratio of drug to polymer was increased, the particle size decreased. The mean particle size of formulations FDRS1-FDRS4, FPRS1-FPRS4, FDS1-FDS4, and FPS1-FPS4 in the ratios of 3:1, 6:1, 9:1 and 12:1 were found to be between 60-44µm, 62-41 µm, 53-34 µm and 55-38 µm, respectively. This could probably be due to the fact that in high drug to polymer ratios, the amount of polymer available per microsponge was comparatively less. Hence less polymer surrounded the drug resulting in smaller microsponges.

The effect of stirring rate on the size of microsponges was studied by photo microscope RXLr-3T (Radical, India). The formulation with the lower drug to polymer ratio (i.e., 3:1) was chosen to investigate the effect of stirring rate on the morphology of microsponges. The stirring rate was varied in the range of 300 to 500 rpm for eudragit RS-100 based formulations and 500 to 1000 for eudragit S-100 based
formulations. The dispersion of the drug and polymer into the aqueous phase and the formulation of microsponge were found to be dependant on the agitation speed. As the speed was increased, smaller spherical microsponges with uniform size were formed. When the rate of stirring was increased 300 - 500 rpm eudragit RS-100 based microsponges, the spherical microsponges were formed with mean particle size of 71 µm - 60 µm and 77 µm - 62 µm for the formulation FDRS1 and FPRS1, respectively. When the rate of stirring was increased 500 - 1000 rpm for eudragit S-100 based microsponges the spherical microsponges were formed with mean particle size of 74 µm - 52 µm and 79 µm - 54 µm for formulation FDS1 and FPS1, respectively.

It was observed that on increasing the volume of internal phase from 5 to 10 ml microsponges were not formed. This may be due to the decrease in viscosity of the internal phase. As the amount of dichloromethane was increased, though the finely dispersed spherical quasi-emulsion droplets were seen in solvent under the agitation, but as the stirring was discontinued emulsion droplets adhered to each other and coalesce. Consequently, no microsponges could be formed. The result suggests that the amount of dichloromethane need to be controlled within an appropriate range to effect not only the formation of quasi-emulsion droplets at the initial stage but also the solidification of drug and polymer in the droplets. Microsponges were formed when 3 to 5 ml of dichloromethane was used.

An increase in amount of polyvinyl alcohol (emulsifying agent) from 0.5 % to 1.0 % w/v resulted in decreased production yield and increased mean particle size. The amount of emulsifying agent significantly effected the production yield and mean particle size. Due to non-ionic nature of the emulsifier some hydrophobic region might have formed which dissolved some of the drug and polymer resulting in lower production yield. An increased amount of emulsifying agent decreased the production yield from 79% to 61%, 72% to 67%, 73% to 65%, 71% to 68% for the formulations FDRS1, FPRS1, FDS1, FPS1, respectively The increase in the amount of emulsifying agent resulted in larger microsponges, probably due to increased viscosity, wherein larger emulsion droplets formed resulting in larger microsponges. An increased amount of emulsifying agent increased the mean particle size from 60 µm to 71 µm, 62 µm to 66 µm, 53 µm to 64 µm, 55 µm to 56 µm for the formulations FDRS1, FPRS1, FDS1, FPS1, respectively.
The prepared microsponge formulations were characterized for angle of repose, Carr’s Index, Hausners ratio, production yield, actual drug content, encapsulation efficiency and mean particle size. The value of angle of repose, Carr’s Index and Hausners ratio was found to be between 14.14-25.05°, 2.39-13.46 % and 1.02-1.14, respectively which showed excellent compressibility and good flowability.

The production yield was found to be between 72-76% for FPRS1-FPRS4, 71-77% for FPS1-FPS4, 70-79% for FDRS1-FDRS4, and 68-77% for FDS1-FDS4. The actual drug content was found to be between 74-91% for FPRS1-FPRS4, 72-89% for FPS1-FPS4, 62-81% for FDRS1-FDRS4, and 67-83% for FDS1-FDS4. The encapsulation efficiency ranged from 82-98%. The mean particle size was found to be between 62-41 µm for FPRS1-FPRS4, 55-38 µm for FPS1-FPS4, 60-44 µm for FDRS1-FDRS4, and 53-34 µm for FDS1-FDS4. The data obtained for various formulations in respect to production yield, actual drug content, and encapsulation efficiency were subjected to t-test at 95% level of significance. No significant difference in relation to these parameters was observed amongst various formulations at p <0.05.

DSC and FTIR studies were carried out on drug(s), physical mixture of drug(s) with different polymers and different microsponge formulations using Shimadzu DSC-60 Thermal Analyzer and Shimadzu Model 8400 FTIR spectrometer, respectively. According to the DSC thermograms, drugs showed sharp endothermic peaks (dicyclomine and paracetamol at 175.97°C and 174.23°C, respectively) which corresponded to the melting point of drug in the crystalline form. In the DSC curve of physical mixture, formulations FPRS1-FPRS4, FPS1-FPS4, FDRS1-FDRS4, and FDS1-FDS4, the characteristic peaks of drug(s) were seen. In FTIR spectra of paracetamol, characteristic N-H stretching band at 3413.77 cm\(^{-1}\), O-H stretching band at 3326.98 cm\(^{-1}\), and carbonyl stretching band at 1654.81 cm\(^{-1}\) were seen and in case of dicyclomine, characteristic C=O stretching band was observed at 1718.45 cm\(^{-1}\), which were in agreement with the reported values. All characteristic peaks of drug(s) were observed in the FTIR spectra of different microsponge formulations namely FPRS1-FPRS4, FPS1-FPS4, FDRS1-FDRS4, and FDS1-FDS4. The result showed that drugs were compatible with polymers. It could also be conferred that microsponge preparation processes did not change the nature of drugs in microsponges.
The different microsponge formulations of dicyclomine and paracetamol were subjected to *in-vitro* release studies using USP XXIV dissolution assembly. It was observed that for each formulation the drug release decreased with increase in the amount of polymer. This may be due to the fact that the release of drug from the polymer matrix takes place after complete swelling of the polymer and as the amount of polymer in the formulation increases the time required to swell also increases. The release showed a bi-phasic pattern with an initial burst effect. In the first hour drug release of different microsponge formulations FPRS1-FPRS4, FPS1-FPS4, FDRS1-FDRS4, and FDS1-FDS4 was noted to be between 16-30%, 17-30%, 15-30% and 19-29 %, respectively. This may be attributed to the drug present in the pores of the microsponges. The overall cumulative percent release for different microsponge formulations FPRS1-FPRS4, FPS1-FPS4, FDRS1-FDRS4, and FDS1-FDS4 at the end of 8 h was found to be between 59-86 %, 53-83 %, 61-94 %, and 56-86 %, respectively.

The correlation coefficient and release rate constant values for zero order, first order, Higuchi and Korsemeyer models were computed. The correlation coefficient values of different microsponge formulations namely FPRS1-FPRS4, FPS1-FPS4, FDRS1-FDRS4, and FDS1-FDS4 were found to be between 0.9729-0.9865, 0.9788-0.9834, 0.9538-0.9733, and 0.9647-0.9720, respectively for zero order model; between 0.9846-0.9934, 0.9896-0.9834, 0.9748-0.9854, and 0.9832-0.9890, respectively for first order model; between 0.9848-0.9957, 0.9915-0.9922, 0.9783-0.9884, and 0.9863-0.9921, respectively for Higuchi model. The R values were much closer to 1 for the Higuchi kinetics. From the correlation coefficient values it is concluded that the drug release from different microsponge formulations follow Higuchi model. Higuchi model explained the matrix diffusion mechanism of drug release. The correlation coefficient values for Higuchi model confirmed that drug release followed matrix diffusion mechanism or Higuchi pattern release. The mechanism of drug release of the all microsponge formulations was studied by fitting the release data to Korsemeyer equation. The n values for formulations FPRS1-FPRS4, FPS1-FPS4, FDRS1-FDRS4, and FDS1-FDS4 was found to be between 0.7939-0.6908, 0.7375-0.6358, 0.7476-0.6989, and 0.7231-0.6199, respectively. The n value for Korsemeyer-Peppas model was found to be between 0.5-1 indicative of non-fickian diffusion.
The *in-vitro* dissolution data was subjected to statistical analysis using ANOVA. The *p* value was found to be 0.5754, 0.5447, 0.5930, and 0.5207 for FPRS1-FPRS4, FPS1-FPS-4, FDRS1-FDRS4, and FDS1-FDS4, respectively. This indicated significant difference (*p*>0.05) amongst various formulation in relation to dissolution behaviour.

The core tablets consisting of microsponges containing 40 mg dicyclomine and 250 mg paracetamol, Na-CMC and magnesium stearate were prepared by direct compression method. The core tablets were evaluated for various parameters like weight variation, thickness, hardness, friability, and drug content.

The average weight of the core tablet formulations CPDRS1-CPDRS4 and CPDS1-CPDS4 was found to be between 438 - 470 and 442 - 461 mg, respectively. The variation in weight was within the range of ±5% complying the pharmacopoeial specifications. The hardness was found to between 4.1 kg/cm$^2$ - 4.8 kg/cm$^2$ indicating satisfactory mechanical strength. The friability of the core tablet formulations were found to be between 0.23 % - 0.79 %. The friability was below 1% which indicated good mechanical resistance. The thickness was found to between 2.76-3.01 mm.

The coated tablets were prepared by compression coating with Pectin:HPMC (80:20) mixture as outer shell. The coated tablet formulations were evaluated for various parameters like weight variation, thickness, hardness, and friability.

The average weights of the coated tablet formulations CPDRS1-CPDRS4 and CPDS1-CPDS4 were found to be between 637 - 670 and 648 - 663 mg, respectively. The variation in weight was within the range of ±5% complying the pharmacopoeial specifications. The hardness was found to between 5.8 kg/cm$^2$ - 6.8 kg/cm$^2$ indicating satisfactory mechanical strength. The friability of the core tablet formulations were found to be between 0.41 % - 0.79 %. The friability was below 1% which indicated good mechanical resistance. The thickness was found to between 3.40 - 3.67 mm.

The developed formulations (CPDRS1-CPDRS4 and CPDS1-CPDS4) were subjected to *in-vitro* drug release studies using USP XX1V dissolution assembly at the stirring rate at 50 rpm and temperature at 37±0.5 °C. The dissolution studies were carried out at first hour in 0.1N HCl, second and third hour in phthalate buffer pH 4.5, fourth and fifth hour in phosphate buffer pH 6.8, sixth hour in phosphate buffer pH
7.4 and after 6th hour in mixture of phosphate buffer pH 6.8 and pectinex Ultra-SPL (1% v/v) in order to simulate the enzymatic action of the colonic bacteria were used.

It was observed that no drug was released in the first six hours. After the lag time of 6 hours, the drug started releasing at 7th hour due to the presence of the pectinex Ultra-SPL. Formulation CPDRS1, CPDRS2, CPDRS3, CPDRS4 released 69%, 88%, 92%, 96% of paracetamol and 76%, 99%, 98%, 99% of dicyclomine, respectively at the end of 12-14 h. Formulation CPDS1, CPDS2, CPDS3, CPDS4 released 76%, 97%, 99%, 99% of paracetamol and 72%, 99%, 97%, 93% of dicyclomine, respectively at the end of 12-14 h.

The results of in-vitro drug release studies showed that pectin: HPMC (80:20) coat could protect the core for 6 hours which correspond to the time to reach the colon and then under the influence of the enzyme, the system started delivering the drug to the proximal colon, main site for bacterial carbohydrate metabolism.

Stability study was carried out at 40 °C ± 2 °C and 75 % ± 5% RH for 3 months. The changes in drug content of different formulations were noted. The obtained data was subjected to t-test at 95% level of significance. No significant difference in relation to drug content was observed amongst various formulation at p <0.05.

The results of the in-vitro drug release and stability studies indicated that the formulations CPDRS1 and CPDS1 could be the potential formulation for targeting the dicyclomine and paracetamol to the colon.

This study presents a new approach for the preparation of modified microsponges as well as a new delivery system with a great potential for colonic drug delivery. The unique compressibility of microsponges offers a new alternative for producing mechanically strong tablets. The colon specific tablet formulations were prepared following two approaches. Both the approaches, using the triggering mechanism of micro-flora activation, represented interesting forms for delivery if the drugs to the proximal part of the colon, avoiding release in the small intestine. The particulate form (microsponges) has been used to provide more uniform distribution of the drug in the colon and help the drug to spread on the colon surface in an appropriate way.
The obtained microsponges exhibited spherical shape, good flowability and excellent compressibility properties. The compression coated formulations prepared using pectin and HPMC in the ratio of 80:20 protected the drug from being released in the stomach and small intestine under *in-vitro* conditions mimicking mouth-to-colon transit.

This study presents a novel colon specific drug delivery system containing dicyclomine and paracetamol microsponges. It is concluded that the microsponges prepared by quasi-emulsion solvent diffusion method can be used successfully for colon specific drug delivery.