INTERNATIONAL JOURNAL OF ADVANCE RESEARCH AND DEVELOPMENT

(Volume3, Issue7)

Available online at: www.ijarnd.com

Formulation and invitro evaluation of colon targeted S.R. tablets of Fenoprofen using novel natural gums

K. L. Deepthi[1], G. V. Radha[2]

[1]Assistant Professor, Sri Venkateswara College of Pharmacy, Etcherla, Andhra Pradesh

[2]Associate Professor, Gandhi Institute of Technology and Management, Visakhapatnam, Andhra Pradesh

ABSTRACT

Colon targeted drug delivery system is capable of protecting the drug in route to the colon i.e. drug release and absorption does not occur in the stomach and small intestine but only released and absorbed once it reaches the colon. Fenoprofen tablets were prepared by wet granulation Technique using different ratios of Fenoprofen with polymers like dikamali gum, karaya gum, gum kondagogu, okra gum, and Eudragit RL100. In the present study, the sustained release tablets were prepared with hydrophilic polymers like gum dikamali along with other natural polymers. Gum dikamali is Gardenia gummifera belonging to the family Rubiaceae, are medium-sized trees growing all over India. The gum-resin oozing out from the leaf buds of these trees is called Dikamali gum. The natural polymer selected for the present study was Dikamali which is a hydrophilic matrix forming agent. Eudragit RL 100 was used as a polymer for targeting the drug to the colon. The invitro drug release studies showed that the drug release was sustained in a better way in the colon for 24hours with dikamali gum in combination with another natural polymer. Invitro dissolution studies of fenoprofen tablets revealed that the formulation F19 containing dikamali gum as a polymer shows maximum drug release at the end of 24hours when compared with the other formulations. Drug release kinetics of the optimized formulation states that the formulation F19 follows zero order drug release with fickian diffusion mechanism.

Keywords— *Colon targeted drug delivery, Dikamali gum, Wet granulation, Natural polymers*

1. INTRODUCTION

Colon-specific drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides[1-4]. Increasing bioavailability via a colonic formulation approach has also been found to be effective in minimizing unwanted side-effects. Different approaches are designed based on prodrug formulation, pH-sensitivity, time-dependency (lag time), microbial degradation and osmotic pressure etc. to formulate the different dosage forms like tablets, capsules, multiparticulates, microspheres, liposomes for colon targeting. The efficiency of the drug delivery system is evaluated using different in vitro and in vivo release studies. The development and the design of colon-specific drug formulations represents a technological challenge as these dosage forms must pass through the upper gastrointestinal (GI) tract in intact form before delivering the drug to the colon. Colon-specific drug delivery does not appear to make much sense at first because of the small area of absorption and the strong barrier properties of the colonic epithelium. Formulations for colonic delivery are, in general, delayed-release dosage forms which may be designed either to provide a 'burst release' or a sustained/prolonged release once they reach the colon. However, the colon has some unique features, which make this organ attractive for site-specific drug delivery. On the one hand, the peptidase activity in the large intestine is significantly lower than that in the stomach and the small intestine and the colonic transit time is much longer than that of the upper GI tract. This allows the delivery of unstable peptide drugs and drugs with a low permeability to this lower intestinal region. On the other hand, the topical treatment of colonic disorders may lead to the reduction of both drug dose and side effects. Fenoprofen is a propionic acid derivative and is a prototypical NSAID used to reduce fever, mild to moderate pain, inflammatory diseases like osteo, rheumatoid, juvenile arthritis and ankylosing spondylitis.

2. MATERIALS AND METHODS

Fenoprofen was obtained as a gift sample from Mylan pharmaceuticals, Sodium alginate, okra gum, karaya gum, Eudragit RL100, gum kondagogu were purchased from S.D. Fine chemicals, MCC, PVP K30, Mg-Stearate, Talc from S.D fine chemicals, Mumbai.

2.1 Methodology

Determination of λmax of Fenoprofen

A solution of Fenoprofen containing the concentration 10 µg/ ml was prepared in different buffers like 0.1N HCL, 6.8pH buffer, 7.4 pH buffer and UV spectrum was taken using Shimadzu (UV-1800) double beam spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Preparation of Fenoprofen tablets

By direct compression method [5-8]

Fenoprofen colon targeted tablets were prepared by direct compression technique using the drug and a variable concentration of dikmali gum alone and along in combinations with okra gum, gum kondagogo and karaya gum, Eudragit RL 100, Lactose, MCC, Mg-sterate, and Talc). The respective powders & optional additives (composition listed in table-5.3) were blended thoroughly with a mortar and pestle. The powder blended was then lubricated with Mg-stearate and purified talc and then compressed on a tablet punching machine. The enteric coating solution was prepared by a simple solution method using 3%, 6% and 9% W / W of Eudragit L100. The PEG (1.5% w/w) was used as plasticizer and acetone and isopropyl acetone was used as a solvent. This mixture was constantly stirred for 1h with paddle mechanical stirrer and the stirred coating solution was again filtered through a muslin cloth to obtain a coating solution.

3. EVALUATION OF FENOPROFEN MICROSPHERES

3.1 Weight variation

Twenty tablets from each formulation were selected at random and average weight was determined. Then the individual tablets were weighed and were compared with average weight[9].

3.2 Hardness

The hardness of the tablet from each formulation was determined using a Pfizer hardness tester.

3.3 Friability

Friability of the tablets was determined using Roche Friabilator. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre-weighed a sample of tablets was placed in the friabilator and was subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (f) is given by the formula.

$$\text{Friability (f)} = (1 - \frac{W_o}{W}) \times 100$$

Where, W_o is the weight of the tablets before the test and W is the weight of the tablet after the test.

3.4 Thickness and diameter

The thickness and diameter of the tablet were carried out using Digital calipers. Three tablets were used for the above test from each batch and results were expressed in millimeter.

3.5 Drug content

Powder one tablets extraction was carried out using 6.8pH buffre. The concentration was determined spectrophotometrically against an appropriate blank. Calculate the content of Fenoprofen specific absorbance As given in IP[10,11].

3.6 *In-vitro* dissolution studies

The release rate of Fenoprofen from the tablet was determined using the United States Pharmacopoeia (USP) dissolution testing apparatus II. The formulated microspheres (F1-F16) were tested for the in vitro dissolution studies for the first 2hrs in 0.1N HCL, as the stomach pH was acidic in nature, then the buffer was replaced with 6.8pH for 5hrs as the intestinal transit time was nearly 5hrs, and then the buffer was replaced with 7.4pH as the colon pH was alkaline in nature. Samples were analyzed by Uv spectrophotometer at 279nm.

3.7 Kinetics of drug release

In short, the results obtained from *in vitro* release studies were plotted in different kinetics models of data treatment as follows:

(i) Cumulative percentage drug release vs. Time (zero order rate kinetics).
(ii) Log cumulative percentage drug retained vs. Time (first-order rate kinetics).
(iii) Cumulative percentage drug release vs. √T (Higuchi's classical diffusion equation).
(iv) Log cumulative percentage drug release vs. Log Time (Peppas exponential equation).

4. RESULTS AND DISCUSSION

4.1 Standard plot of Fenoprofen

The standard graph of Fenoprofen was analyzed in different buffer mediums using 0.1N HCL, 6.8 and 7.4pH phosphate buffers. And it shows that the Fenoprofen in all these three buffers obeys beers law as its regression value was found to be 0.999 in all the three buffers.

4.2 Drug-polymer interaction (FTIR) study

From the drug and polymer compatibility studies it was found that the characteristic peaks that were observed in the pure drug were found to be in the optimized formulation of the tablets so that it was confirmed that the drug haven't any interactions with polymers we have used.

Post-compression parameters:

(i) The average weight of the fenoprofen colon targeted tablets were found to be in the range of 397.99±0.04 to 401.22±0.54mg.
(ii) The thickness of the fenoprofen colon targeted tablets were found to be in the range of 3.14±0.02 to 3.69±0.36mm.
(iii) The hardness of the fenoprofen colon targeted tablets were found to be in the range of 4.23±0.36 to 5.88±0.24kg/cm2.
(iv) Friability of the fenoprofen colon targeted tablets was found to be in the range of 0.11±0.11 to 0.86±0.22%
(v) Drug content of the fenoprofen colon targeted tablets were found to be in the range of 82.69±0.10 to 96.56±0.54%.

4.3 Invitro dissolution studies

The formulated fenoprofen colon targeted tablets (F1-F20) were tested for the in vitro dissolution studies for the first 2hrs in 0.1N HCL, as the stomach pH was acidic in nature, then the buffer was replaced with 6.8pH for 5hrs as the intestinal transit time was nearly 5hrs, and then the buffer was replaced with 7.4pH as the colon pH was alkaline in nature.

The colon targeted tablets were prepared by using dikamali gum alone and in combinations with natural polymers like karaya gum, okra gum, gum kondagogu.

The F1 trail was formulated using dikamali gum alone at a concentration of 25mg/tab, shows maximum drug release at the end of 6hrs as the concentration of polymer was very low which is not sufficient for sustaining the drug release whereas F2 trail was formulated using karaya gum as a sustained release polymer at a concentration of 25mg/tab shows maximum drug release at the end of 8hrs, in a sustained manner, but it wasn't designed to release pattern as per our criteria so that the concentrations of the polymers were increased further. F3 trail was formulated using gum kondagogu as a matrix former at a concentration of 25mg/tab, shows maximum drug release at the end of 6hrs. While F4 trails were formulated using okra gum at the same concentration as the above trails but none of the trails shows sustained drug release. So the concentrations of the polymers were further increased to retard the drug release. Formulations F5-F8 were formulated using the polymers as that of used in F1-F4, but in these trails, the polymer concentration was increased from 25mg/tab to 50mg/tab. The drug release from the formulations was found to be as F5 shows at 8^{th} hour and F6 at the 10^{th} hour, F7 at the 12^{th} hour, whereas F8 at the 12^{th} hour. From the above dissolution studies i.e., from F1-F8 it was observed that none of the above formulations doesn't show sustained drug release as per our aim and objective. So to evaluate the matrix forming capacity of the dikmali gum as a sustained release polymer, based upon the individual polymer trails i.e., from F1-F8.

From the above dissolution studies, it was clearly observed that the natural polymers we have used alone didn't sustain the drug release. So now dikmali gum was used along with other natural polymers in different ratios to sustain the drug release. The F9 formulation containing Dikmali gum and karaya gum in 25:25 ratio shows maximum drug release at the end of the 12^{th} hour. An F10 formulation containing Dikmali gum and gum kondagogu in 25:25 ratio shows maximum drug release at the end of the 12^{th} hour. An F11 formulation containing Dikmali gum and okra gum in 25:25 ratio shows maximum drug release at the end of the 12^{th} hour. Among the formulations F9-F11 that were formulated using dikmali gum and natural gums in combination, it was observed that the drug release was not sustained for a long time. So the polymer concentrations were further increased from 25:25 to 37.5:37.5. F12 trail containing dikamali: karaya gum shows maximum drug release at the end of 24 hrs, but in case of F13 and F14 using gum kondagogu and okra gum along with dikmali gum didn't sustain the drug release up to 24hrs.

Among these F12 sustains the drug release up to 24hrs. To optimize the sustained release polymer concentration, further trails were formulated using 50:50 ratios of dikmali gum and natural polymers, but due to higher polymer concentration, the drug release was retarded more than the normal. So F12 trail was considered as the optimize concentration of dikmali gum and karaya gum as sustained release polymer. Eudragit concentration was further increased to 6% and it retards the drug release up to 4-5hrs, to optimize the Eudragit concentration further trail was coated with 9% Eudragit, and it retards the drug release for more than 6hrs.

So 6% Eudragit was considered as the optimal concentration to retard the drug release.

Based upon the dissolution studies it was observed that F19 formulation suits for colon targeted drug delivery.

Table 1: Formulation table of Fenoprofen tablets

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
Drug(mg)	200	200	200	200	200	200	200	200
Dikmali gum(mg)	25	--	--	--	50	--	--	--
Karaya gum	--	25	--	--	--	50	--	--
Gum kondagogu	--	--	25	--	--	--	50	--
Okara gum	--	--	--	25	--	--	--	50
Lactose	119	119	119	119	94	94	94	94
MCC	40	40	40	40	40	40	40	40
Talc	8	8	8	8	8	8	8	8
Mg.stearate	8	8	8	8	8	8	8	8
Total Wt:	400	400	400	400	400	400	400	400

Table 2: Formulation table of Fenoprofen micropsheres

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
Drug(mg)	200	200	200	200	200	200	200	200
Dikmali gum(mg)	25	--	--	--	50	--	--	--
Karaya gum	--	25	--	--	--	50	--	--
Gum kondagogu	--	--	25	--	--	--	50	--
Okara gum	--	--	--	25	--	--	--	50
Lactose	119	119	119	119	94	94	94	94
MCC	40	40	40	40	40	40	40	40
Talc	8	8	8	8	8	8	8	8
Mg.stearate	8	8	8	8	8	8	8	8
Total Wt:	400	400	400	400	400	400	400	400

Table 3: Evaluation parameters of Fenoprofen microspheres

Formula	Average weight	Hardness	Thickness	Friability	Drug content
F1	399.86±0.12	5.12±0.24	3.20±0.28	0.26±0.04	84.36±0.36
F2	399.45±0.26	5.98±0.36	3.62±0.16	0.34±0.27	88.02±0.22
F3	398.79±0.58	5.38±0.12	3.45±0.29	0.24±0.22	86.22±0.02
F4	397.99±0.04	5.12±0.08	3.20±0.22	0.72±0.36	82.69±0.10
F5	399.66±0.32	5.36±0.34	3.18±0.16	0.68±0.24	84.21±0.26
F6	398.69±0.12	5.22±0.12	3.26±0.10	0.56±0.12	88.08±0.51
F7	399.17±0.56	4.83±0.26	3.14±0.02	0.82±0.18	93.39±0.29
F8	399.55±0.01	5.14±0.24	3.38±0.35	0.48±0.36	87.22±0.02
F9	399.91±0.12	5.12±0.12	3.29±0.12	0.38±0.24	90.14±0.16
F10	400.02±0.18	5.16±0.58	3.49±0.34	0.21±0.26	90.56±0.54
F11	399.62±0.22	5.44±0.12	3.67±0.26	0.24±0.54	88.54±0.28
F12	399.44±0.35	5.52±0.33	3.25±0.29	0.64±0.21	92.98±0.16
F13	399.96±0.12	5.32±0.16	3.40±0.54	0.76±0.16	90.28±0.33
F14	400.28±0.36	5.14±0.24	3.16±0.26	0.72±0.18	92.22±0.28
F15	399.87±0.87	5.28±0.18	3.32±0.22	0.58±0.44	96.56±0.54
F16	400.19±0.24	4.23±0.36	3.54±0.17	0.86±0.22	92.84±0.33
F17	400.02±0.08	5.16±0.24	3.48±0.15	0.46±0.16	93.16±0.26
F18	418.28±0.12	5.42±0.11	3.56±0.26	0.52±0.20	94.22±0.15
F19	412.26±0.13	5.26±0.24	3.69±0.36	0.18±0.18	95.12±0.29
F20	421.22±0.54	5.88±0.24	3.74±1.52	0.22±0.16	93.28±0.24

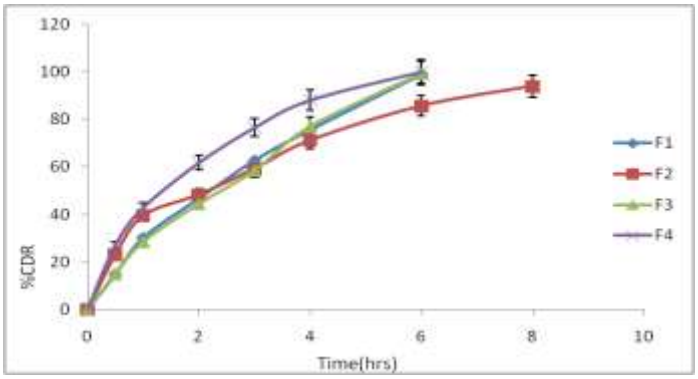

Fig. 1: *in vitro* drug release studies of F1-F4 formulations

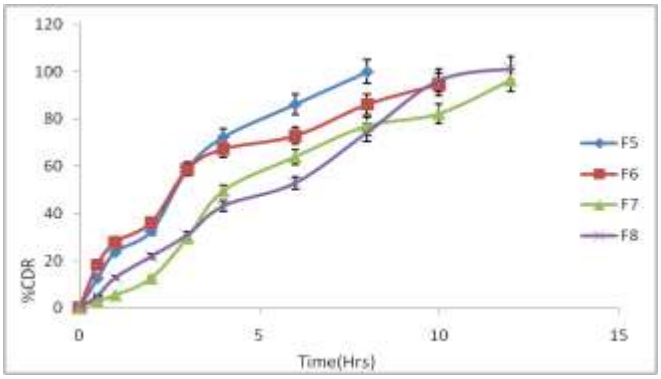

Fig. 2: *in vitro* drug release studies of F4-F8 formulations

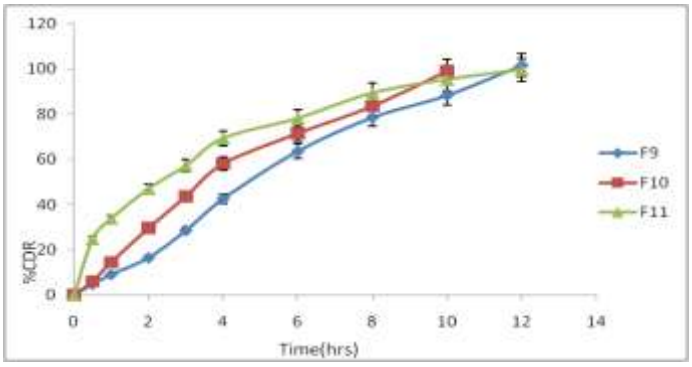

Fig. 3: *in vitro* drug release studies of F9-F11 formulations

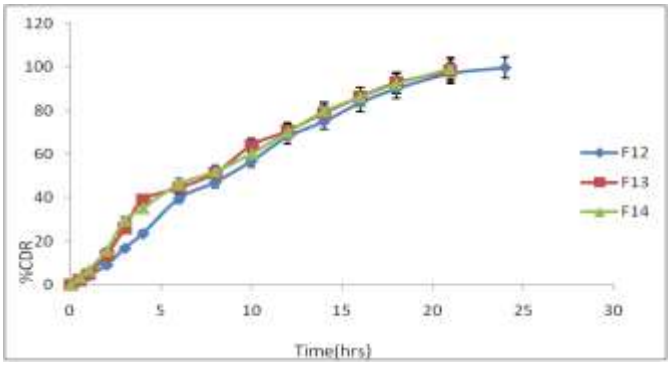

Fig. 4: *in vitro* drug release studies of F12-F14 formulations

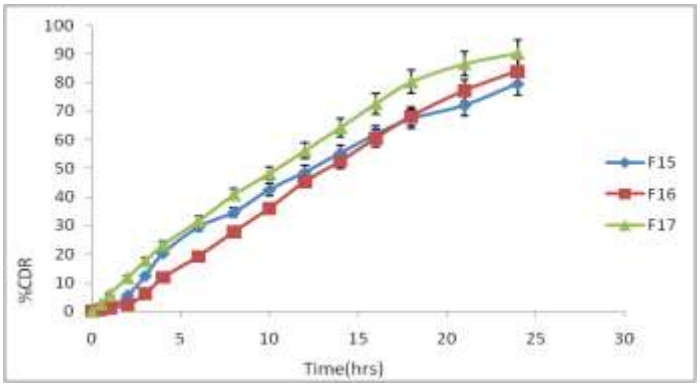

Fig. 5: *in vitro* drug release studies of F15-F17 formulations

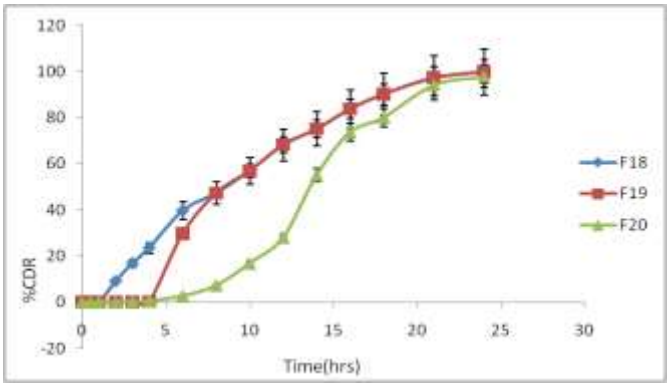

Fig. 6: *in vitro* drug release studies of F18-F20 formulations

Table 4: Kinetic data of Fenoprofen microspheres

R^2 values					n values
Formulation	**Zero-order**	**First order**	**Higuchi**	**Korsmeyer - Peppas**	**Korsmeyer-Peppas (n)**
F19	0.986	0.791	0.953	0.610	1.854

5. CONCLUSION

Tablets of Fenoprofen was formulated by wet granulation technique using different drug: polymer concentrations and by using different natural polymers like karaya gum, gum kondagogu and okra gum along with Dikamali gum. The invitro dissolution data for best formulation F19 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F4 shows R^2 value 0.986. As its value nearer to the '1', it is confirmed as it follows the Zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport. The 'n' value is 1.854 for the optimized formulation (F19) i.e., n value was > 0.89 this indicates super case transport. The release kinetics for the optimized formula is shown in the table.

6. REFERENCES

[1] Amitha Shetty, Mohd Azharuddin, A R.Shabaraya., development, and evaluation of Fenoprofen microspheres as colon targeted drug delivery system, International Journal of Innovative Drug Discovery, 2015; 5(1): 7-13.

[2] Kuldeep H Ramteke, L. K. Nath.,Formulation, Evaluation, and Optimization of Controlled Release Hydrogel Microspheres for Colon Targeted Drug Delivery, J. Pharm. Sci. & Res., 2012; 4(2): 1739-1747.

[3] Ankit Vajpayee 1, Suresh Fartyal1, Alok Pratap Singh1 Sajal Kumar Jha2., formulation and evaluation of colon targeted curcumin microspheres using natural polymers, Journal of Pharmaceutical Research And Opinion, 1, 2011; 4: 108–112.

[4] Mahajan Anil Arunb, Pathak Naresh Shriramb, Upadhyay Schitnand a, Pratap Vijay a, Mondal Md. Sahidullah a, Formulation and Evaluation of Colon Targeted Drug Delivery of an Anti-Amoebic Drug international journal of pharmaceutical innovations, March-April 2012; 2(2).

[5] Rana mazumder.et.al., formulation and in vitro evaluation of natural polymers based microspheres for colonic drug delivery, International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 2(1).

[6] Apparao potu. et.al, formulation and evaluation of Fenoprofen calcium compressed coated tablets for colon specific drug delivery, Asian Journal of Pharmaceutical and Clinical researchvol, 2011; 4(2).

[7] Anuj chawla. et.al, Eudragit S-100 coated Sodium alginate microspheres of naproxen Sodium: Formulation, optimization and in vitro evaluationacta Pharm, 2012; 62: 529–545.

[8] M. J. Barea, Encapsulation of Liposomes within ph responsive microspheres for Oral Colonic Drug Delivery, Hindawi Publishing Corporation International Journal of Biomaterials, 2012; 458712: 8.

[9] Kishori L. Deore*, Nilima A. Thombre, Paraag S. Gide., Formulation and development of tinidazole microspheres for colon targeted drug delivery system, a journal of pharmacy research, 2013; 6: 15(8e1): 65.

[10] N. R. KOTAGALE*, Ranitidine Hydrochloride-loaded Ethyl Cellulose, and Eudragit RS 100 Buoyant Microspheres: Effect of ph Modifiers, Indian Journal of Pharmaceutical Sciences, and November-December 2011.

[11] Uzma Farooq*, Design and Development of Multi Particulate System for Targeted Drug Delivery Using Natural Polymer, Pharm Anal Acta, 2015; 6: 5.

BIOGRAPHY

K. L. Deepthi
M. Pharmacy
Assistant Professor
Sri Venkateswara College of Pharmacy, Etcherla, Andhra Pradesh

Dr. G.V. Radha
M. Pharmacy, Ph.D.
Associate Professor
Gandhi Institute of Technology and Management, Visakhapatnam, Andhra Pradesh

