Research Paper www.ijcps.com

International Journal of
Chemical and Pharmaceutical Sciences
2013, Mar., Vol. 4 (1)

ISSN: 0976-9390
IJCPS

Formulation and *In-Vitro* evaluation of mebeverine hydrochloride colon targetted micropellets for the treatment of irritable bowel syndrome

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ABSTRACT

The present study in formulation and evaluation of Mebeverine hydrochloride micropellets. Mebeverine hydrochloride which is used as a anti spasmodic drug to treat irritable bowel syndrome. The pellets were prepared by pan coating powder layering method by using nonpareil seeds in core pellets and were coated with HPMC K4M, Eudragit S100 and Eudragit L100 in different ratios to form a film coat over the pellets. The prepared micropellets were evaluated with various evaluation methods such as drug content, loose surface crystal studies, in-vitro drug release studies, kinetic studies and stability studies as per ICH guidelines were performed. The formulated extended release micropellets were prepared by powder layering technique. In these formulations containing 20mg of Mebeverine hydrochloride and developed employing Eudragit L100, Eudragit S100 and HPMC K4M. The dissolution study of F7 formulation was concluded as the best formulation among other formulations, which showing the most desired drug release. It will be considered as optimized formulation. No significant change was observed in the drug content physical properties and dissolution rate of these micro pellets after the storage period of three months at 40±2ºc and 75±5%RH.

Keywords: Mebeverine hydrochloride, Irritable bowel syndrome, Colon specific, Pan coating, Powder layering technique, Micropellets.

1. INTRODUCTION

Pellets are of great interest to the pharmaceutical industry for variety of reasons. Pelletized products not only offer flexibility in dosage form design and development, but are also utilized to improve safety and efficacy of bioactive agents. The aim of the present study was to develop a stable, pharmaceutically equivalent and delayed release micro pellet formulation of Mebeverine hydrochloride [1].

Irritable bowel syndrome (IBS) is a disorder characterized most commonly by cramping, abdominal pain, bloating, constipation and diarrhea. Mebeverine Hydrochloride is an anti-spasmodic drug given orally and topically (rectal route) for the treatment of irritable bowel disease. These compounds act directly on the gut muscles at the cellular level to relax them. Mebeverine HCl which used to normalizes the small bowel motility. It is having a short biological half life of 2.5hrs, plasma protein binding 75% and rapidly absorbed after oral administration with peak plasma concentration occurring in 1-3hrs [2].

There has been an increasing interest in the development of site-specific systems for the release of drugs in the colon. The advantages and necessity of colon targeting to provide more effective therapy for colon related disease, such as irritable bowel syndrome, colon cancer and inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, have been well recognized. Patients with irritable bowel syndrome and ulcerative colitis exhibited accelerated transit through different regions of the colon. The colon as a site for drug delivery, offers distinct advantages on account of a near neutral pH, a much longer transit time, relatively low proteolytic enzyme activity and a much greater responsiveness to absorption enhancer [3, 4].

2. MATERIALS AND METHODS

2.1. Materials

Mebeverine hydrochloride was received as a gift sample from Bindu Pharma Pvt.Ltd., Andhrapradesh. Eudragit L100, Eudragit S100 and HPMC K4M were obtained from natco pharma Ltd., andrapradesh. Nonpareil seeds were obtained from richer health care, Hyderabad.

2.2. Preparation of mebeverine micropellets

The micropellets of Mebeverine hydrochloride were prepared by pan coating powder layering technique. The formulation of delayed release micropellets of Mebeverine hydrochloride were done by using polymers HPMC K4M, Eudragit L100 and Eudragit S100 Table 1.

2.3. Drug loading

Nonpareil seeds (lactose pellets) were sieved through 30#40 sieves and pellets was taken for drug loading from total batch size, required quantity of drug was taken and dispersed in binder solution (PVP 30) stirred for 10min and nonpareil seeds were loaded onto conventional coating pan and pan was rotated at 36 rpm and spray of binding solution was started at the rate of 10gm solution/min. The solution spray rate and dosing rate was kept constant throughout the process. The drug loaded micropellets were dried at 45^0 C for 8 hours in stainless steel tray drier. Check moisture content, it should be below 1%. Then pass the pellets through sifters to remove fines. And the batch was termed as F1. Same process followed to manufacture the batches F2, F3, F4, F5, F6, F7, F8 and F9 [5].

2.4. Coating with polymers

Drug loaded micropellets were coated with coating polymers(HPMC K4M, Eudragit L100, Eudragit S100)in different ratios.

2.5. Evaluation of micropellets

2.5.1. Appearance

The pellets were visually observed for physical appearance of pellets.

2.5.2. Particle size

Particle size distribution of micropellets was determined by optical microscopy using calibrated ocular eye piece. Fifty micropellets were evaluated and the experiment was performed. Geometric mean diameter was then calculated using the equation [6].

$$Xg=10 X [(n_iXlogX_i)/N]$$

X_g is geometric mean diameter, n_i is number of particles in the range, X_i is the midpoint of range, N is total number of particles analyzed.

2.5.3. Angle of repose

The dried micropellets were allowed to fall freely through a funnel fixed at 1 cm on a horizontal surface and the angle of repose (θ) was measured.

$$\theta = \tan^{-1}h/r.$$

Where h is the height of the heap, r is the radius.

2.5.4. Drug content

200mg pellets were weighed and powdered, a quantity of powder equivalent to 20 mg of each formulation was transferred to a 25 ml volumetric flask and 15 ml water is added. The drug is extracted in water by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the liquid is filtered. The drug content was determined by measuring the absorbance at 263 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated [7].

Table - 1: Composition of Colon Targeted Micropellets of Mebeverine hydrochloride

Ingredients (mg/capsule)	Formulations Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Mebeverine HCl	20	20	20	20	20	20	20	20	20
PVP K30	6	6	6	6	6	6	6	6	6
Lactose pellets	160	150	140	160	150	140	140	150	160
HPMC K4M	6	8	10	6	8	10	10	8	6
Eudragit S100	8	16	24	-	-	-	12	8	4
Eudragit L100	-	-	-	8	16	24	12	8	4
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total fill weight	200	200	200	200	200	200	200	200	200

2.5.6. Scanning electron microscopy

Morphological examination of the surface and internal structure of the dried beads was performed by using a scanning electron microscope (SEM). Micropellets before dissolution only subjected to SEM study since, after dissolution the pellets become swollen palpable mass. Photographs were taken within the range of 50-500 magnification.

2.5.7. *In-Vitro* drug release studies

The release of drug from the developed formulation in the GIT was determined using USP dissolution type II apparatus. The drug release studies were carried out in pH 1.2 for 2 hrs, in pH 6.8 for next 3 hrs and in pH 7.4 for next 7 hrs at 37± 0.50ºC and 100 rpm. At regular time interval, 5 ml of sample was withdrawn from the dissolution medium and replaced with equal volume of fresh medium. After filtration and appropriate dilution, the samples were analyzed at 263nm for Mebeverine HCl against blank using UV-Visible spectrophotometer. The amount of drug present in the samples was calculated using standard curve [8].

2.5.8. Release drug data model fitting

The suitability of several equation that are reported in the literature to identify the mechanisms for the release of drug was tested with respect to the release data up to the first 50% drug release. The data were evaluated according to the following equations: [6]

Zero order model

$Mt = M0 + K0t$

Higuchi model11

$Mt = M0 + KH\ t\ 0.5$

Korsmeyer-Peppas model12

$Mt = M0 + KKtn$

Where Mt is the amount of drug dissolved in time t. M0 is the initial amount of the drug. K0 is the Zero order release constant, KH is the Higuchi rate constant, K is a release constant and n is the release exponent that characterizes the mechanism of drug release.

2.5.9. STABILITY STUDIES

Stability studies were carried out at 40°C / 75% RH for the optimized formulation for 3 months. The micropellets were stored at 40°C/75% RH as per ICH guidelines and various parameters (drug content and drug release profile) were monitored periodically for 3 months[9].

3. RESULTS AND DICUSSION

The micropellets were prepared by powder layering technique using different polymers did show significant results during their evaluation.

The appearance shows the pellets being spheroid in shape and showing smooth surface of pellets. Results were shown in table 2 and Figure 2-4.

The size of micro pellets found to be in the range of 500µm to 790µm and it was observed that increase in concentration of coating polymer particle size of the micro pellets significantly increased. The average particle size is highest for F8. The particle size distribution is uniform and narrow. Results were shown in table 3.

Angle of repose ranged from 23.31 ± 0.04 to 25.92 ± 0.15. The flow properties of micropellets in all formulations exhibit good flow. Results were shown in table 4.

Drug content was found to be uniform among different batches of micropellets and ranged from 98.6 to 99.75 %. These results showed that the all formulations having percentage drug content within the specified limits as per IP. Results were shown in table 4.

Loose surface crystal study was an important parameter giving an indication of the amount of the drug on the surface of the micropellets without proper entrapment. It also conforms net drug loss during process is minimal. With the increase in the copolymer concentration % LSC decreased significantly owing to high entrapment of drug in the dense network of polymer. Results were shown in table 4.

The scanning electron microscope shows the pellets being spheroid in shape. Surface depression was noted at the point of contact on the drying paper. On comparison of the pellets prepared from polymer s in high concentrations more roughness was observed with Eudragit polymers. Eudragit S100 produces more smooth surface area as compared to others. Results were shown in Figure 2-4.

The *in vitro* drug release data of all the formulations were fitted in zero order, first order and peppas model and the rate constant (k), correlation coefficient (R^2) and n values were compared to know the mechanism of drug release from the micropellets. Comparing the R^2 values of all formulations, it is evident that F1,F2,F3,F4,F5 formulations following peppas release, F6,F7 formulations following zero order release and F8,F9 formulations following first order release. The formulation F7 showing high cumulative % drug release after 12 hrs was found to be 89.37%, which contains eudragit L100 and eudragit S100.

The drug gets released by passive diffusion. Results were described in table 5-6 and Figure 1.

The selected formulations F7 were subjected to stability studies as per ICH guidelines. There were no change in drug content and cumulative percentage drug release at 40°C / 75% RH. All the parameters were within the limit after 90 days. Results were shown in Figure 5 and Figure 6.

Table - 2: General appearance study of micropellets

Parameters	Placebo	F1-F3	F4-F6	F6-F9
Composition	-	Eudragit L100	Eudragit S100	Both Eudragit L100 and Eudragit S100
Shape	Spherical	Spherical	Spherical	Spherical
Size by visualization	Small	Large than control	Large in size	Large in size
Colour	Creamish white	More white than control	White pellets	White pellets
Stickiness	None	None	None	None
Odour	No	No	No	No

Table - 3: particle size for various formulations of micropellets

Formulations Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Particle size (µm ± S.D)	500 ±0.50	640 ±0.32	690 ±0.41	610 ±0.45	670 ±0.43	658 ±0.32	759 ±0.34	789 ±0.54	775 ±0.36

All the values are expressed as a mean ± SD., n = 3

Table - 4: Physico-Chemical Properties of micropellets

Formulations Code	Angle of Repose (°)	Drug Content (%)	Loose surface crystal (%)
F1	24.23±0.02	99.05±0.02	3.201
F2	24.23±0.02	99.30±0.02	2.360
F3	24.48±0.04	98.6±0.015	1.990
F4	25.06±1.06	98.85±0.030	3.891
F5	23.93±0.19	99.2±0.028	3.237
F6	25.18±0.33	98.65±0.025	2.569
F7	25.92±0.15	99.05±0.036	1.786
F8	24.72±0.15	99.65±0.040	1.463
F9	23.31±0.04	99.75±0.026	1.589

All the values are expressed as a mean ± SD., n = 3

Table - 5: *In-vitro* drug release data of Formulation F1-F9

Medium	Time (hrs)	Cumulative drug Release (%)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
0.1N HCl	0	0	0	0	0	0	0	0	0	0
	1	6.19	5.61	5.91	6.77	6.34	5.91	5.62	5.76	6.05
pH 6.8 phosphate buffer	2	6.99	12.09	11.24	14.84	13.40	12.45	11.96	12.53	13.11
	3	11.02	15.70	14.70	18.44	17.29	15.91	15.42	17.87	17.74
	4	17.51	22.62	21.19	25.22	23.92	22.54	21.76	25.36	25.24
	5	21.11	26.08	24.94	29.11	27.82	26.86	25.66	29.98	29.85
pH 7.4 phosphate buffer	6	51.39	56.21	51.61	61.12	58.38	55.70	59.82	61.83	61.57
	7	71.57	77.26	74.24	80.87	78.57	76.17	79.00	80.438	80.31
	8	74.60	80.86	78.28	84.04	82.89	78.48	83.61	82.59	83.63
	10	75.76	82.16	79.29	86.20	85.34	82.23	87.65	86.99	86.95
	12	77.05	83.46	80.30	88.37	87.65	85.11	89.37	87.43	88.25

Table - 6: Different Kinetic models for Formulations F1-F9

Code	Zero order		First order		Higuchi		Korsemayer's-Peppas		Best fit model
	R^2	K_0 (mg/h^{-1})	R^2	K_1 (h^1)	R^2	K ($mg\ h^{-1/2}$)	R^2	n	
F1	0.9367	0.7878	0.9358	0.0082	0.8481	2.1188	0.9387	1.1424	Peppas
F2	0.9362	0.7907	0.9352	0.0082	0.8435	2.1220	0.9375	1.1688	Peppas
F3	0.9363	0.7610	0.9352	0.0079	0.8410	2.0394	0.9413	1.1892	Peppas
F4	0.9395	0.8917	0.9386	0.0093	0.8484	2.3955	0.9411	1.1533	Peppas
F5	0.9407	0.8782	0.9398	0.0092	0.8444	2.3530	0.9408	1.1848	Peppas
F6	0.9423	0.8490	0.9414	0.0088	0.8441	2.2727	0.9416	1.1975	Zero order
F7	0.9456	0.7139	0.9455	0.0074	0.8724	1.9362	0.9221	0.9358	zero order
F8	0.9466	0.7171	0.9468	0.0074	0.8883	1.9568	0.9387	0.9131	First order
F9	0.9985	0.7197	0.9487	0.0074	0.8869	1.9613	0.9356	0.9099	First order

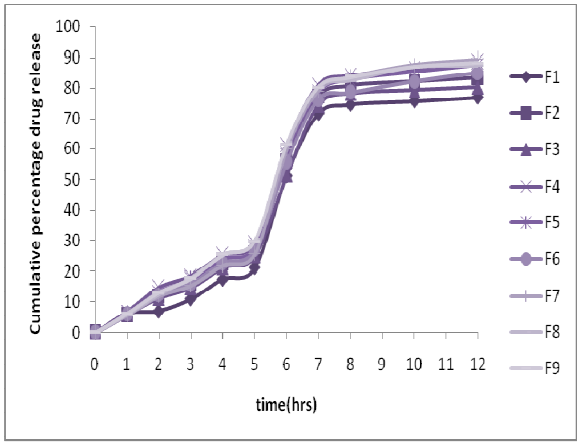

Figure - 1: Cumulative % Drug release profile of formulation F1 – F9.

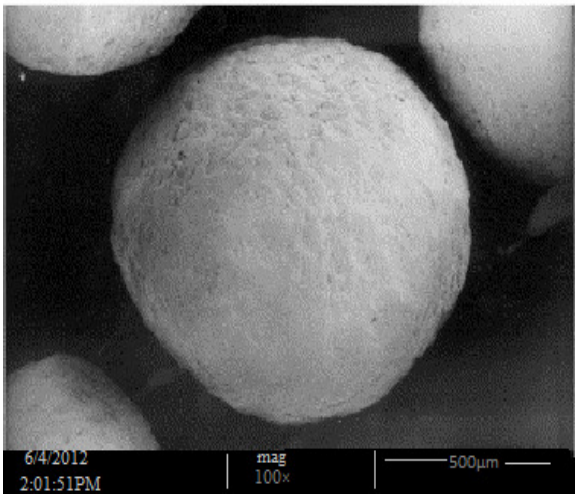

Figure - 2: Scanning electrone microscopy of Mebeverine HCl loaded micropellets with Eudragit L100.

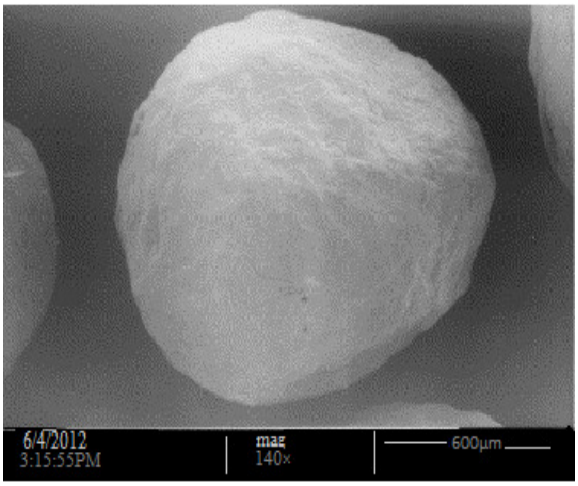

Figure - 3: Scanning electrone microscopy of Mebeverine HCl loaded micropellets with Eudragit S100.

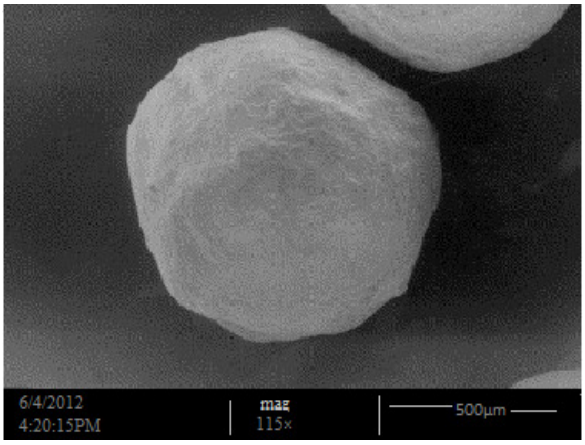

Figure - 4: Scanning electrone microscopy of Mebeverine HCl loaded micropellets with Eudragit S100 and Eudragit S100.

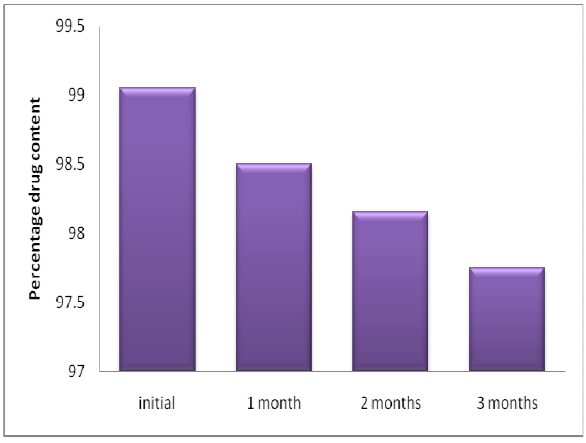

Figure - 5: Comparison of drug content for formulation F7 with initial and different periods of stability.

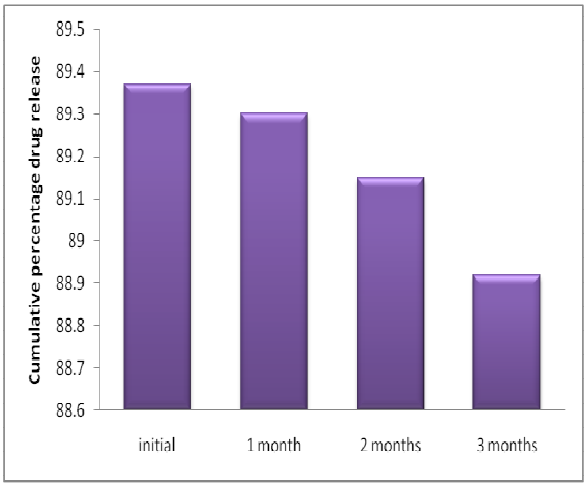

Figure - 6: Comparison of cumulative percentage drug released at the end of 12 hours for formulation F7with initial and different periods of stability.

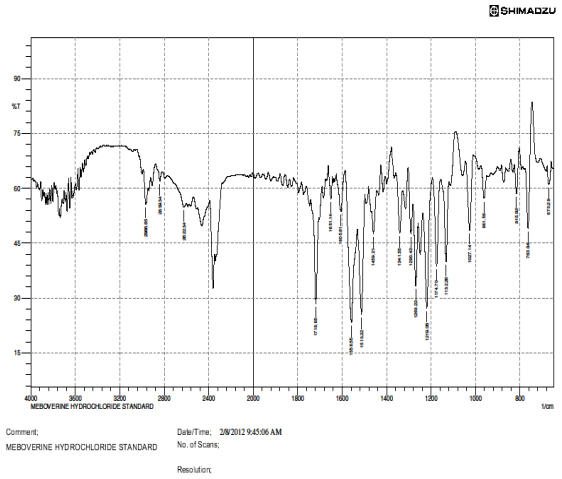

Figure - 7: FTIR spectrum of Mebeverine hydrochloride.

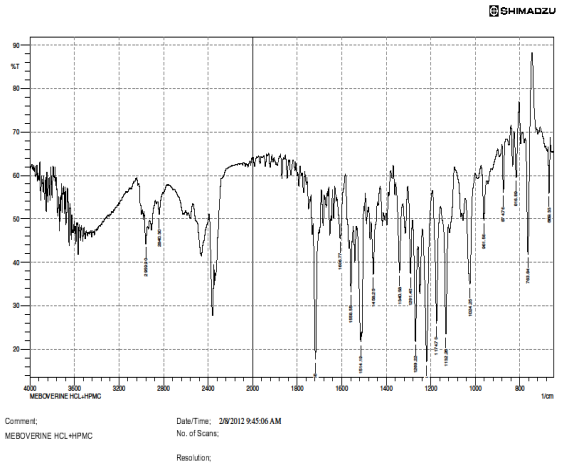

Figure - 8: FTIR spectrum of Mebeverine hydrochloride with HPMC K4M.

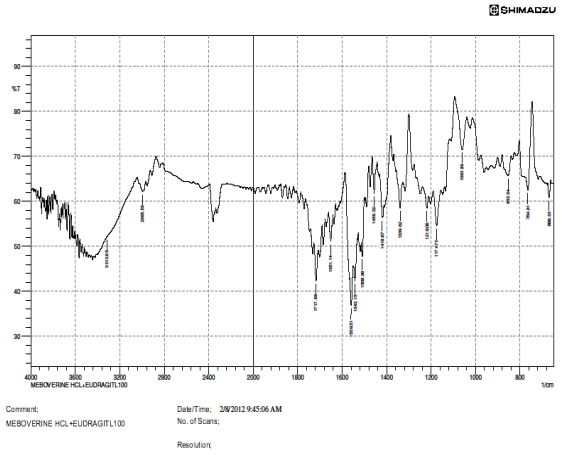

Figure 9: FTIR spectrum of Mebeverine hydrochloride with Eudragit L100.

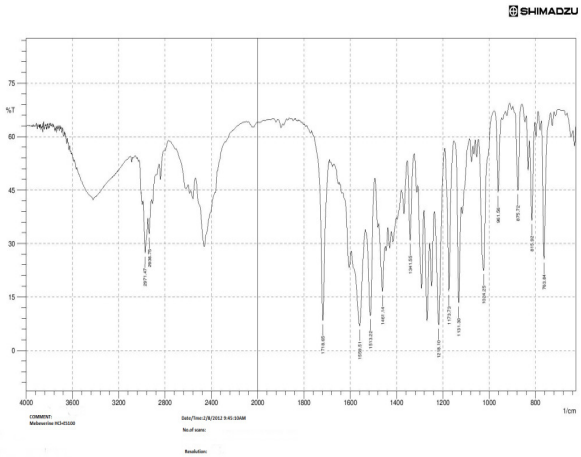

Figure - 10: FTIR spectrum of Mebeverine hydrochloride with Eudragit S100.

Acknowledgement

We express our sincere thanks to our management, Adhiparasakthi College of Pharmacy, melmaruvathur, kanchipuram for their support to providing the facilities to complete the work. We also extend our thanks to Bindu pharmaceuticals Pvt. Ltd., Andhrapradesh, Richer Healthcare for providing us gift samples of drug and polymers.

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