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Original Research Article

Formulation, evaluation, and optimization of the omeprazole magnesium multi-unit particulate controlled release tablets using different concentrations of polymers

Akshay Parihar[1,*], **Bhupendra Gopalbhai Prajapati**[2], **Kiran Patel**[2], **Himanshu Paliwal**[2,3]

[1] *Faculty of Pharmaceutical Sciences, The ICFAI University, Baddi, Himachal Pradesh, India*
[2] *Dept. of Pharmacy, Shree S.K. Patel College of Pharmaceutical Education and Research, Mehsana, Gujarat, India*
[3] *Drug Delivery System Excellence Center, Prince of Songkla University, Hat Yai, Songkhla, Thailand*

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ABSTRACT

Multi-Unit Particulates (MUPs) with matrix pellets are used to develop controlled release products of various active pharmaceutical ingredients. They may allow improvement in solubility and thereby bioavailability of poorly soluble drugs. Omeprazole magnesium is a derivative of benzimidazole which belongs to the group of proton pump inhibitors that exhibits degradation in gastric acid with short biological life and variability in bioavailability. The drug degradation problem was overcome by the coating of pellets with enteric coating agents which disperse in the gastrointestinal tract more homogenously than single units with a rapid transit time. Pellets were compressed to reduce the tampering risk and transportation difficulty through the esophagus. The coating was done with the bottom spray technique. A batch of 5% concentration of binder optimized for a tablet affects the disintegration of the tablet. A cushioning agent was employed to optimize the acid resistance with a concentration of 12% and the release profile was depicted in pH 6.8 phosphate buffer followed by 0.1N HCl for 2 hours. The optimized batch was evaluated for acid resistance, similarity factor, SEM, dissolution, and stability studies which exhibited maximum resistance in gastric pH with abrupt release in duodenal pH because of the multi-particulate approach.

1. Introduction

Drug administration using the oral route is preferred for most patients as a route of choice. Many modified-release formulation technologies are now offering active means for optimization to overcome the limitations of the drug release kinetic profiles.[1] We have used multi-particulate dosage forms which offer various advantages over the conventional formulations in terms of transit times through the GI tract, dispersion characteristics, and reduced chances of irritation in gastric mucosa.[2]

The oral Multi-Unit Particulates Drug Delivery Systems (MUPDDS) have become very important in current times because of their ability to control the release of drugs as well as the facilitation capability for the modified drug release profiles.[3] Preparation of multiple unit dosage provides an advantage that it helps to decrease the inter and intra-subject variability of absorption, this helps to conclude that delayed-release multiple unit particulate system serves as a promising approach for the drug delivery. Cushioning agent is also used to overcome the enteric film breakage of the pellets during tableting which will eventually lead to degraded form in an acidic environment.[4]

* *Corresponding author*.
E-mail address: akshay.parihar20@gmail.com (A. Parihar).

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Omeprazole magnesium is used as a model drug in the present work. It belongs to the group of PPIs and suppresses the secretion of gastric acid by specifically inhibiting the H+/K+-ATPase in the gastric parietal cell. It specifically acts on the proton pump and blocks the final step of acid production which eventually reduces gastric acidity. Omeprazole is indicated for the treatment of Peptic ulcer disease, gastroesophageal reflux disease, and Zollinger-Ellison syndrome.[5]

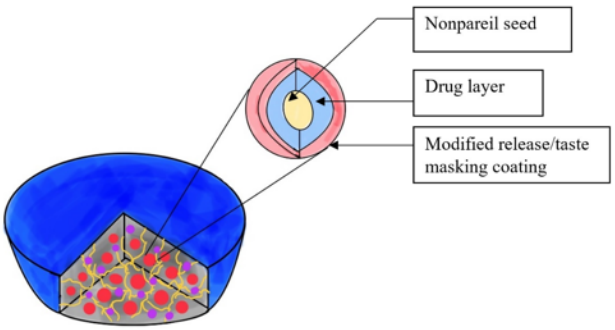


Fig. 1: Reservoir pellet MUP

2. Material and Methods

2.1. Materials

Omeprazole magnesium was provided as a gift sample by Raks pharma Pvt. Ltd, Ahmedabad, India. HPMC -3cps & HPMC -6cps were obtained from Hanns G. Werner Ltd, India, and Shin Etsu Ltd, India respectively. Eudragit L 100 55 and Plasacryl T20 were provided from Evonik Pvt. Ltd, India. Polyvinyl alcohol was obtained from Merck Ltd, Mumbai, India. PEG 6000 was obtained from Clariant Chemicals Pvt. Ltd, India. SSF was provided by JRD Pharma Ltd, India.

2.2. Methods

2.2.1. Drug layer optimization of binder concentration, barrier agent, and talc concentration and compression of pellets in tablets

Seal-coated pellets were taken for drug coating using the HPMC 6cps binder to prevent the sticking of the drug particles to the seal-coated pellets. Omeprazole magnesium solution was used for drug coating on the seal-coated pellets using IPA as solvent and DCM as the binder in the Fluid bed processor. Drug layering was examined by maintaining the parameters of Inlet temperature of 40-45°C, Bed temperature of 30-32°C, Blower drive speed at 35-40 CFM, atomization at 1.8-2.5 bar, and spray rate at 5-20 rpm. To separate the drug layer and enteric coating later and an intermediate layer of the rapidly disintegrating polymer was formed using PVA as it was capable of forming water-soluble firm formation along with Magnesium stearate and Talc. The barrier layer was evaluated on the parameters of inlet temperature of 40-45°C, bed temperature of 30-35°C, blower drive speed at 45-50 CFM, atomization at 2.1-2.2 bar, and spray rate of 6-8 rpm. Different batches were formulated in varying concentrations of PVA to talc on the pellets layered with the drug with the use of an 8% barrier coating agent. The excipients used for the formulation were povidone K29/32, PEG 6000, MCC-102, and SSF. Two different ratios of pellets to excipients were taken for trial, whose values were 30:70 and 25:75. Optimization of this ratio helps in reducing damage to pellets because less no. of pellets will be required and the crushing of them will also be prevented. Batch T3 and T4 gave 8 min and 12 min respectively which were found satisfactory, but due to the higher amount of binder, the T5 batch failed. Batch T4 was having 5% concentration optimization and was taken for further processing based on disintegration time, assay, and friability tests.

2.3. Enteric coating layer

Eudragit L100 55 polymer was used to provide an enteric coating for the omeprazole magnesium. To control agglomerates during the coating process Plasacryl T20 was used due to its good anti-tracking properties. Triethyl citrate was used in the coating process to provide greater flexibility to the film. Talc was also used to avoid the sticking of polymer-coated beads. Three batches were prepared which were having the same concentration of enteric coating agent on the already prepared barrier layer which gave the results as shown in Table 3. Optimized enteric-coated pellets EC3 Batch was used for the compression of pellets. By using the direct compression method, a threshold of at least 30% of the extra-granular materials was added to provide support and cushioning. The coated subunits were freely embedded in the matrix without segregation to form coherent tablets. The process parameters were, Inlet temperature at 40-4°C, Bed temperature at 30-32°, blower drive speed of 47-51 CFM, Atomization at 2.0-2.2 bar, and spray rate at 56 rpm was maintained.

2.4. Evaluation of omeprazole magnesium Mup's tablet

2.4.1. Physical description

Enteric-coated tablets prepared were evaluated for their color, shape, and flow properties.

2.4.2. Density

For density measurement, the USP-I auto-tapped density apparatus was used

Table 1: Formulation of drug coating on seal layered pellets, barrier layer using different barrier agent concentrations on drug layered pellets, and compression of 70% enteric-coated pellets using different pellets: excipients ratio

Ingridients	**D rug coating on seal layered pellets** **D1**	**D2**	**D3**	**D4(20%)**	**D5(40%)**	**D6(60%)**	**D7 (70%)**
	mg	mg	mg	mg	mg	mg	mg
Seal coated pellets	22.47	22.47	22.47	22.47	22.47	22.47	22.47
Omeprazole Mg	20.6	20.6	20.6	20.6	20.6	20.6	20.6
HPMC 6cps	4.49	4.49	4.49	4.12	8.24	12.36	13.1
IPA (75%)	50%	65%	75%	qs	qs	qs	qs
DCM (25%)	50%	35%	25%	qs	qs	qs	qs
Barrier layer using different barrier agent concentrations on drug layered pellets							
Ingridients	B1 (Without talc and Mg stearate)	B2 (With talc and Mg stearate)	B3 (4%)	B4(6%)	B5(8%)	B6 (PVA: talc: :(1:1))	B7 (PVA: talc: :(1:2))
	mg	mg	mg	mg	mg	mg	mg
Drug layer pellets	51.31	51.31	51.31	51.31	51.31	51.31	51.31
PVA	3.08	3.08	2.05	3.07	4.10	4.10	4.10
Talc (PVA: Talc:: 1:1)	-	3.08	2.05	3.07	4.10	4.10	8.2
Magnesium stearate	-	0.12	0.08	0.12	0.16	0.16	0.16
Water	qs	qs	qs	qs	qs	qs	qs
Compression of 70% enteric-coated pellets using different pellets: excipients ratio							
Ingredients	T1 Mg	T2 Mg	T3(3%) Mg	T4(5%) Mg	T5(7%) Mg	T6 (10%) Mg	T7(12%) Mg
Enteric-coated pellets	108.41	108.41	108.41	108.41	108.41	108.41	108.41
MCC (FLOCEL) 102	237.76	305.67	312.22	305.72	299.22	273.2	266.69
Plasdone k29/32	12.65	16.26	9.76	16.26	22.76	16.26	16.26
PEG6000	-	-	-	-	-	32.52	39.03
Sodium stearyl fumarate (1%)	2.52	3.3	3.25	3.25	3.25	3.25	3.25

Table 2: Formulation of enteric coating using different concentrations of enteric coating on barrier-coated pellets

I ngredients	**EC1 (60% weight gain)**	**EC2 (65% weight gain)**	**EC3 (70% weight gain)**	**EC4 (75% weight gain)**
	mg	mg	mg	mg
Subcoated pellets	63.77	63.77	63.77	63.77
Eudragit L 100 55	27.33	29.61	31.89	34.16
Talc (20%)	5.47	5.92	6.38	6.83
TEX (10%)	2.73	2.96	3.18	3.42
Plasacrylate T (10%)	2.73	2.96	3.18	3.42
Methanol (80%)	qs	qs	qs	qs
Water (20%)	qs	qs	qs	qs

2.4.3. Particle size analysis

Sieve analysis was done by using the USP sieve shaker apparatus which gave uniform pellets, that was useful for further operations.

2.4.4. Sphericity of pellet

The sphericity of the pellet is represented by the aspect ratio which is responsible for its flow properties. The height and width of the pellets were determined with the help of an optical microscope. For best spheric, the aspect ratio should be very near to 1. It was calculated by the following formula:[6]

$$\text{Aspect ratio} = \frac{length\ of\ pellets}{width\ of\ pellets}$$

2.4.5. Acid resistance

The pellets were filled in capsules and the test was performed on 6 units. The IV dissolution test was carried out using USP dissolution testing apparatus II (paddle type). The dissolution test was performed with the aid of 300ml of 0.1N hydrochloric acid(pH-1.2), at 37±°C and was set at 100 rpm for 2 hours. At regular intervals of time, samples were withdrawn and replaced with a fresh dissolution medium. The samples were filtered through a 0.45 μ membrane filter and they were measured for absorbance using a UV/Vis double beam spectrophotometer and were assayed for drug content.

Table 3: Assay and acid resistance of batch EC1, EC2, EC3, EC4

Batch	Acid resistance	Assay
EC1	11±1.64	99.5±1.36
EC2	5.9±2.36	102±1.65
EC3	1.5±1.79	101.5±1.24
EC4	1.0±2.58	101±2.54

2.5. Evaluation of multiunit particulate tablets

Maps were evaluated for their appearance by their discoloration and degradation of drugs by the visual method. Schleuniger digital tester was used for measuring the hardness. The force was measured in kilograms, newtons, or kilopascal units. Triplicate determination was made. Friability was assessed by the Roche friabilator (camp-bell electronics, Mumbai). 20 tablets of known weight($W_\circ$) were dedusted in a drum for a fixed period and weighed (W) again. The loss in the weight is calculated in terms of percentage and this should not be less than 1% which was done in a triplicate manner using the following formula;[7]

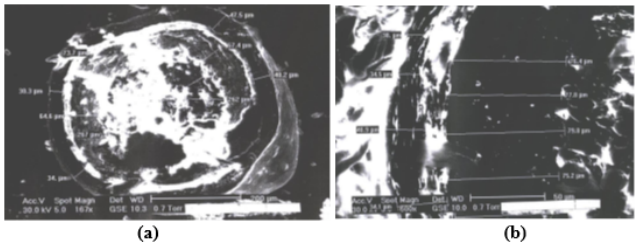
$$\%\text{friability} = 1 - \frac{w}{w_\circ} \times 100.$$

Vernier calipers were used for the determination of thickness and diameter. Twenty tablets were weighed on Mettler Toledo digital weighing balance and determinations were made in triplicate.[8] USP disintegration apparatus was used for the determination of disintegration time for six tablets of the formulation at 37.5°C. The enteric-coated tablets of Omeprazole magnesium were tested for their drug content. It is performed by measuring the active content of 10 individual units. The optimized formulation was put into a stability chamber which was maintained at 40°C and 75% relative humidity for 1 month. The formulations were evaluated at the end of the study for weight, Assay, DT Friability, drug content, acid resistance, in-vitro release profile, and all physical parameters of tablet.[9]

3. Result and Discussion

3.1. Scanning electron microscopy

The pellets were assessed for visualization before and after compression using a scanning electron microscope (Jeol-5610) by taking the photographs of enteric-coated intact pellets and the distribution of pellets in the matrix. Scanning Electron Microscopy of the product has shown that the pellets were spherical and were not crushed during the compression.



(a) (b)

Fig. 2: a) SEM micrograph of cut pellet, b) SEM microphotograph of the side view of the cut pellet

3.2. FTIR studies

FT-IR spectroscopy was carried out to study drug-polymer interaction. Some characteristic peaks of omeprazole magnesium were observed between 2800-3000 cm^{-1} and 1600-1650 cm^{-1} due to the presence of OCH3 six-membered cyclic ring respectively. It proved that excipients did not affect the characteristic peaks of the drug and the drug did not lose its properties as it has not shown any type of interaction with polymers and excipients.[10]

3.3. Differential scanning calorimetry study

Drugs and their formulations were characterized with the help of DSC thermograms. The thermogram of formulation T8 exhibited the exothermic slight broad peaks at 205.20°C which is equal to the pure drug. It was concluded that the properties of the drug were not lost and no interaction was observed with the excipients and polymers.

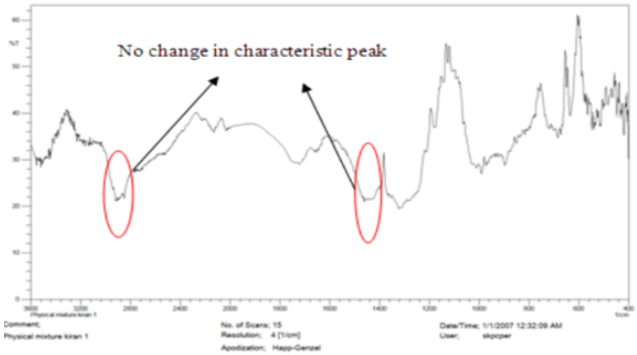


Fig. 3: FTIR of omeprazole magnesium MUP's tablet

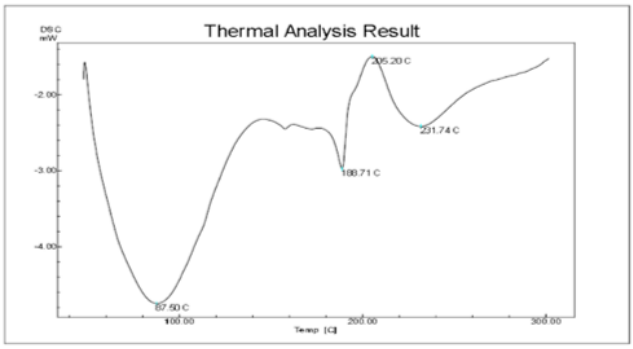


Fig. 4: DSC study of Omeprazole magnesium MUP's tablet

3.4. *Curing effect on drug release*

Curing is a very crucial parameter in pellet formulation. As the curing of enteric-coated pellets is done at different time intervals and temperatures the dissolution will be retarded. Optimized Batch EC3 was taken for the study of the curing effect on the pellets. The enteric-coated pellets curing for 30 min, 1hr, 2hr, and 4hr. The % drug release at 30 min, 1 hr, 2hr, 3h,r, and 4hr was found to be 98.7±1.96, 96.4 ±3.08, 94.5 ±1.30, and 91.5 ±1.05. There was no effect of different time intervals observed on the drug release profile but as time increases the dissolution was slightly decreased. So finally curing the pellets for 1hr at 45 ºC.

3.5. *Enteric coating layer*

The barrier layer place lets coated with different concentrations of barrier enteric coating as the enteric layer prevents the drug from acidic environment. A batch EC1, EC2, EC3 and EC4 formulated with different % weight gain 60%,65% ,70% and 75% respectively. All batches were evaluated for assay, % drug release, and acid resistance test. The assay of all batches EC1, EC2, EC3, and EC4 were found to be 99.5±1.36, 102.0±1.65, 101.5±1.24, and 101.1±2.54 respectively. The Assay of all batches was acceptable and found within the range. The Assay is determined after the drug layering steps and the

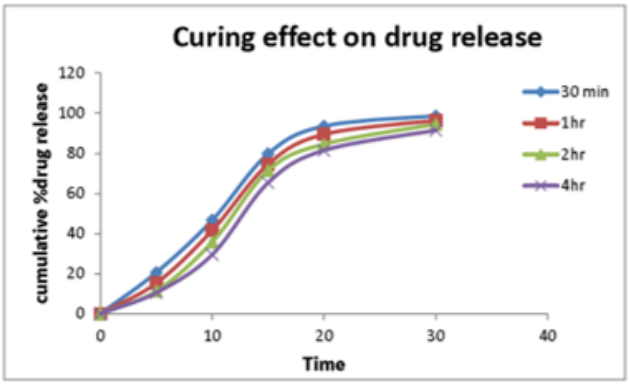


Fig. 5: Comparative in vitro drug release profile of curing effect of batch EC3

risk of enteric coating to impact assay is low. Acid resistance test is done in 0.1N HCL for 2hr. The acid resistance of batches EC1, EC2, EC3, and EC4 were found to be 11±1.64,5.9±2.36,1.5±1.79 and 1.0±2.58 respectively. A batch EC1 failure in the acid resistance test may be due a to lower % of weight gain on pellets. Batches EC2, EC3, and EC4 comply with the acid-resistant test (less than 10%). EC3 and EC4 batches show better acid resistance than EC2 batches.

Content uniformity of optimized batches.Table 4

3.6. *Dissolution profile*

The % release of batches T6, T7, T8, and innovator was found to be 90.5%,94.5%,99.8%, and 95.8±1.87 respectively at 30 min in 6.8 pH phosphate buffer. The T8 batch showed lower acid resistance and a higher release profile than the T7 batch. There was no effect of the cushioning agent on drug release occurs. Cushioning agent affecting the acid resistance test. The assay, % drug rel, ease, and acid resistance of batch T7 match with Innovator. A batch T7 with 12% concentration optimized on basis of assay, % drug release, and acid resistance test result and result ints match with Innovator.

The % release of batches T6, T7, T8, and innovator was found to be 90.5%,94.5%,99,.8%, and 95.8±1.87 respectively at 30 min in 6.8 pH phosphate buffer. T7 batch showed higher acid resistance and lower release profile than the T8 batch. Cushioning agents affected the acid resistance test particularly. The assay, %drug release, and acid resistance of innovator matched with T7 batch with 12% optimized concentration.

3.7. *Release kinetics*

It can be inferred from the results that the release rate data of all batches of MUP's tablets formulated was fitted to the horse Mayer Peppas model square root release kinetics as indicated by the highest value of r2. In the case of the T6

Table 4: Result of content uniformity of batches T5, T6 and T7

Unit	Uniformity of content (%)		
	T5	**T6**	**T7**
1	91.2	112.1	111.2
2	88.3	108.3	118.9
3	94.6	111.3	114.5
4	89.5	109.8	123.5
5	90.5	110.1	114.6
6	98.9	108.5	105.8
7	91.2	107.4	109.6
8	98.6	108.3	104.6
9	101.5	105.4	112.5
10	91.7	104.9	110.7
Mean ± SD	93.6±4.55	108.61±2.33	112.59±5.69

The content Uniformity of batches T6, T7, and T8 was found to be 93.6 ± 4.55, 108.61 ± 2.33, and 112.59 ± 5.69. A batchT7 and T8 pass the content Uniformity test.

Table 5: Dissolution profile of batch T5, T6 and T7 in phosphate buffer

Time	**T5**	**T6**	**T7**	**Innovator**
0	0	0	0	0
5	14.8±1.24	21.5±1.94	30.6±2.41	18.5±2.15
10	34.6±2.21	44.2±3.07	52.8±3.15	40.2±3.04
15	56.4±2.67	65.9±1.60	76.4±3.07	68.4±1.62
20	81.5±3.45	89.4±2.51	95.4±2.41	92.1±2.51
30	90.5±3.08	94.5±1.64	99.8±1.34	95.8±1.87

Table 6: Release kinetics of formulation

Batch no.	R^2Value Zero order	First order	Hixon-crowell cube root model	Higuchi model	Korse mayer peppas model	Slope(n) value for korse mayer peppas model
T6	0.920	0.969	0.861	0.961	0.968	1.063
T7	0.887	0.954	0.834	0.945	0.960	0.872
T8	0.870	0.947	0.826	0.936	0.958	0.702

Table 7: Stability study of optimized batch (T7)

Condition	**Initial**	**1 month**
Weight	433.64mg	433.64mg
Assay	101.2±1.57%	98.6±2.45%
Disintegration test	13±2.51min	11±1.61min
Friability	084±1.56%	0.8±1.38%
Content uniformity	108.61±2.33%	99.38±1.98%
Hardness	8.5±1.54kp	8.1±1.64kp
Acid resistance	7.4±2.35%	7.8±1.76%
% Drug release in phosphate buffer	94.5±1.64%	97.5±1.54%

batch, it was found to be 1.063 which confirms that the drug release mechanism was erosion. The T7 and T8 batch data of. 812 and 0.0702 respectively confirm that the drug release mechanism was fiction diffusion. The commercial product has both methods of drug release.

The stability studies confirmed that the formulation is satisfactory. There was no observation of any significant changes, and the results fall into the acceptance criteria for 1 month.

The accelerated stability study was carried out at 40°C±2°C/75% RH ±5% For 1months Optimized batch T7 was kept in HDPE bottles 1 month for the above conditions sample were analysed for percentage Assays, percent drug releases in phosphate buffer 6.8, Acid resistance, hardness, friability, and content uniformity. The stability studies of the formulations were found to be satisfactory. No significant changes were observed.

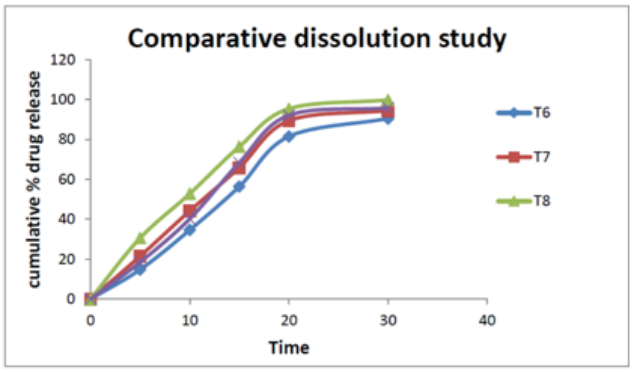


Fig. 6: Comparative in vitro drug release profile of batches T6, T7, T8, and innovator

4. Conclusion

The multi-unit particulate system contained in the tablet was successfully developed and evaluated by the use of various polymers, binder agents, and cushioning agents. The selection of final tablets with different coating layers was done carefully to prevent the rupture of the coating and to maintain the uniformity, hardness, rapid disintegration, and acid resistance of the tablet. The pellet size, the force of compression, cushioning agent, and pellet: excipient ratio were the key variables of the formulation. The Formula of omeprazole magnesium was successfully optimized with a very minimum amount of variation in the map system to maximum gastric resistance which showed immediate release in the duodenal pH.

5. Source of Funding

None.

6. Conflict of Interest

None.

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Author biography

Akshay Parihar, Assistant Professor https://orcid.org/0000-0002-9597-2800

Bhupendra Gopalbhai Prajapati, Professor https://orcid.org/0000-0001-8242-4541

Kiran Patel, Research Scholar https://orcid.org/0000-0003-0678-6000

Himanshu Paliwal, Post Doctoral Fellow https://orcid.org/0000-0001-5438-9881

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