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FORMULATION, OPTIMIZATION AND EVALUATION OF ORAL ANTIBIOTIC FORMULATION TO INCREASE PEDIATRIC COMPLIANCE

Nandini Banerjee*, Sushma Singh

Pharmaceutics, Dr. L. H. Hiranandani College of Pharmacy, C.H.M campus, Ulhasnagar-03, Mumbai, Maharashtra, India.

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***Correspondence for Author:**
Nandini. Banerjee
Pharmaceutics, Dr. L. H. Hiranandani College of Pharmacy, C.H.M campus, Ulhasnagar-03, Mumbai, Maharashtra, India.
banerjeenandini89@gmail.com

ABSTRACT

The objective of the current work was to formulate floating microspheres of cefpodoxime proxetil and then make them to orally disintegrating minitablet to increase the patient compliance amongst the Pediatric Patient Population. The antibiotic drug was coated with polymers HPMC K15 M and Ethyl Cellulose. The coat masked the bitter taste of the drug and also provided a sustained drug release over a period of 12hrs. This coated drug particles were then formulated into Orally dispersible Minitablets. The tablet batches were optimized for their dispersion time using different superdisintegrants at different concentrations. The superdisintegrants tried out were Crosscarmellose sodium and Sodium Starch Glycolate. The parameters evaluated included Hardness, Friability, dispersion time and in-vitro drug release over a period of 12hrs. The batches were also subjected to Stability study over a Period of 6 months at 45^0C/ 75% RH.

Keywords: Taste masking, Factorial design, Dispersion time, Panel testing, HPLC.

INTRODUCTION

Of the world's total patient population a considerable number comprises of pediatrics. Hence special preferences must be given to formulate dosage forms specifically for them. The common ailments seen in children are mainly related to respiratory and digestive tract disorders. as low as 53%, indicating that children frequently fail to take medications properly. Non compliance can lead to: Persistent symptoms, Need for additional doctor visits or even

hospitalization, Worsening of condition, Need for additional medications, increased healthcare cost, Development of resistant organism in cases of infectious diseases. (1)
Antibiotics are one of the most often prescribed drugs for children's diseases. Their use has become so common that not much thought is given to their need for use, their side effects and precautions to be observed during the treatment.

ODTs differ from traditional tablets in that they are designed to be dissolved on the tongue rather than swallowed whole. Mini- tabs are small tablets with a diameter typically filled into a capsule or occasionally further compressed into larger tablets. Mini- tab could also offer a solution to the current issue in the pharmaceutical industry representing a lack of dosage forms which are suitable for paediatrics. Minitablets combine the advantages of multiparticulate dosage forms with the established manufacturing technique of tableting. Additional benefits of Minitab's include excellent size uniformity, regular shape and smooth surface, there by offering an excellent substrate for coating with modified release polymeric system. They can be produced via direct minor equipment modification. For example, in order to increase production speeds multiple tip tooling has been employed routinely. Furthermore, Minitabs can be coated using pan or a fluid bed apparatus. (2, 3)

Organoleptic properties are important consideration for development of orally disintegrating tablets. Taste is the ability to detect the flavor of substances like food, drugs etc. Taste is now became an important factor governing the patient compliance. . It is important to understand that only soluble portion of drug can generate the sensation of taste. Coating the drug with a suitable polymeric film can reduce solubility in saliva by creating a physical barrier between drug and the taste buds and taste of active could be masked. Coating agents employed include gelatin, povidone, HPMC, EC, beeswax, carnauba wax, acrylics and shellac. (4, 5)

Cefpodoxime proxetil is a commonly used antibiotic in pediatrics upto 12 years of age. Cefpodoxime proxetil is an orally administered, extended spectrum, semi-synthetic β- lactum antibiotic of cephalosporin class. Cefpodoxime proxetil is prodrug; its active metabolite is cefpodoxime. After oral administration cefpodoxime proxetil is absorbed from the gastrointestinal tract and de-esterifies to active metabolite cefpodoxime. Over the recommended dosing range (100 to 400 mg) only 50% of administered cefpodoxime dose was absorbed systemically. Also the drug has only 2 to 3 hours half life. Thus by coating it with polymers we can get sustained effect. (6, 7)

MATERIALS AND METHOD

MATERIALS

CEFPODOXIME PROXETIL was provided as a gift sample from CIPLA Pvt. Ltd, Mumbai, India. The Polymers Hydroxypropyl methyl cellulose K 15 M (HPMC K15 M), HPMC K100M and Ethyl Cellulose (EC) was obtained as gift sample from Colorcon Pvt. Ltd, Goa. Microcrystalline cellulose (MCC) and Crosscarmellose Sodium (CCS) was supplied by JRS Pharma, Germany. All other ingredients were of Pharmaceutical grade and were obtained from S.D. Fine Chemicals.

METHOD

Coating of the drug

The drug molecules were coated with the polymer HPMC K15 M and Ethyl cellulose in a ratio of 1:1. The drug and polymers were dissolved in common organic solvent to get a uniform solution. This solution was then slowly added to a non solvent like water. The system was applied with agitation using overhead stirrer at 1100 rpm. The drug molecules get coated with the polymer due to solvent evaporation process. (8, 9, 10)

Preparation of Orally Disintegrating Minitablets

All the ingredients i.e. coated drug, Superdisintegrant, Mannitol, Sweetener etc. were weighed properly and sieved via Sieve no.16. All the ingredients were geometrically mixed and then lubricant was added. The hardness of the compression machine was adjusted. The mixture was then directly compressed with 5mm flat faced punches. The tablet was stored in tightly closed container and evaluated. (11, 12) The various batches of Microspheres formulated are given in the Table 1

Table 1: Composition of Different Batches for Different Concentration of Different Superdisintegrant

Ingredients	CCS 0.5%	CCS 2%	CCS 5%	SSG 2%	SSG 4%	SSG 5%
Microspheres equivalent to	100mg Drug	100mg Drug	100mg Drug	100mg Drug	100mg Drug	100mg Drug
Super disintegrant	0.5%	2%	5%	2%	4%	5%
Aspartame	2%	2%	2%	2%	2%	2%
Mannitol	5%	5%	5%	5%	5%	5%
Vanilla	2%	2%	2%	2%	2%	2%
MCC	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Talc	1%	1%	1%	1%	1%	1%

Optimization of orally disintegrating Minitablets

The independent variable used for the studies were Concentration of Crosscarmellose Sodium and Hardness and the response studied was Dispersion time of the tablets.

The Disintegration time of the minitablet was optimized by varying the independent variables; Concentration of Crosscarmellose Sodium and Hardness of the tablet selected for the preparation.

Concentration of Crosscarmellose Sodium: 0.5, 2, 5%

Hardness: 2, 3, 4 kg/cm^3

EVALUATION

- **Preformulation studies**

  The Preformulation studies involved the following evaluation

- Excipient compatibility
- Calibration curve determination

Compatibility Study of Drug and Polymers

FTIR studies: Compatibility of Cefpodoxime Proxetil with polymers used to coat the drug was studied by FTIR analysis. The different samples evaluated were plain drug, drug mixture with different polymers over a period of 30 days, physical mixture and final Minitablet formulation. The compatibility studies were carried out by testing the samples in accelerated stability conditions of 45^0C and 75%RH for duration of 1 month using FTIR (Shimadzu IR Affinity) with KBr pellet method

Calibration Curve Determination

Determination of λmax: The 10 ppm solution of Cefpodoxime Proxetil was prepared and then scanned in UV-Vis spectrophotometer over a range of 400nm-200nm to determine the λmax of the drug.

Preparation of Calibration Curve (Linearity): The standard calibration curve of drug was prepared by using 0.5% SLS solution.

i] Standard solution: 10mg of Cefpodoxime Proxetil was dissolved in 10ml solution of buffers to get a 1000ppm solution.

ii] Stock solution: From standard solution 1ml was taken and further diluted to 10ml to get a solution of 100ppm. Then aliquots were so taken to get solutions of 1, 5, 10, 15, 20, 25 ppm concentrations.

The absorbance of the prepared Cefpodoxime Proxetil solution was measured at 263nm in Shimadzu UV-Vis 1800 spectrophotometer against the blanks. Then the graphs of Concentration vs. Absorbance were plotted. The Standard Plot data of Cefpodoxime Proxetil in buffer solution is reported.

- **Evaluation Of ODT Minitablets (13,14,15)**

Thickness

Ten tablets from each formulation were taken randomly and their thickness was measured with a vernier calliper. (Aerospace)

Hardness

Hardness (Diametric Crushing force) is a force required to break the tablet across the diameter. The hardness of the tablet is indication of its tensile strength. The tablet should be stable to mechanicals stress during handling and transportation. The degree of hardness varies with the different types of tablets. The hardness of orally disintegrating tablets is generally lower than the conventional tablets. The hardness for 10 tablets was tested using Monsanto Hardness tester. It is expressed in Kg/cm^2.

Uniformity of Weight

Twenty tablets were selected randomly. Tablets were weighed individually and average weight was calculated. Then deviation of each tablet from average weight was calculated and percent deviation was computed. The uniformity of weight was evaluated using the USP specifications.

In all the formulations the average tablet weight is approximately 100mg thus 10% variation is the limit.

Wetting time

A piece of tissue paper (10.75×12 mm) folded twice was placed in a culture dish containing 6 ml of simulated saliva (phosphate buffer pH 6.8). A tablet was carefully placed on the surface of tissue paper and the time required for simulated saliva to reach the upper surface of the tablet was noted as the wetting time. It is studied with the help of Amaranth dye.

Friability

Friability was determined taking tablets equivalent to a weight of approximately 6.5gms. Tablet samples were weighed accurately and placed in friabilator (Roche friabilator). After the given specification (4min at 25rpm), loose dust was removed from the tablets. Finally the tablets were again weighed. The loss in weight indicates the ability of the tablets to withstand this type of wear. The %Friability was calculated using following equation:

% Friability = (Initial weight – Final weight) / Initial weight X 100

Drug content

Ten tablets from each batch were powdered. The sample equivalent to 100mg of drug was transferred to a volumetric flask. 10ml methanol was added to dissolve the drug and then the volume was adjusted with pH 1.2 buffer. It was mixed and filtered. Further dilutions were made and the solution was analyzed against the blank by UV spectrophotometer at 263nm. (UV 1800, Shimadzu)

Dispersion time

a. In vitro:

The in vitro dispersion time of the Minitablets were determined by using glass beakers.

Using beaker

The disintegration was carried out in a beaker consisting of a 200ml medium. The medium of simulated saliva was maintained at 37^0C. Only one tablet was tested at a time and was considered to be disintegrated when completely dispersed fragments were observed.

b. *In vivo*

In vivo disintegration time was judged in 10 healthy male volunteers for each batch of tablets. The volunteers were previously well-versed for purpose of the study. Prior to the test the volunteers were instructed to rinse their oral cavity with distilled water. Each volunteer was asked to place one tablet on the tongue. Volunteers were strictly told not to chew or swallow the tablets, though licking was allowed. The end point for disintegration was taken when there was no lump left in the oral cavity. After the test was finished, volunteers were told to rinse there mouth properly.

***In Vitro* drug release**

The in vitro dissolution of all the batches were carried out in pH 1.2 buffer as dissolution

medium using USP Type II apparatus (TDL-08L, Electrolab) at 75rpm. The temperature was maintained at 37±0.5^{0}C. The dissolution was carried out for 12hrs. The absorbance of the samples at different time intervals was obtained using UV visible spectrophotometer at 263nm. The sampling volume was 5ml which was then reconstituted with the blank buffer. The time points included were 0min, 15min, 30mins, 45min, 1hr, 2hr, 3hr, 4hr, 5hr, 6hr, 7hr, 8hr, 9hr, 10hr, 11hr and 12hr.

MATHEMATICAL MODELLING OF KINETIC RELEASE

In order to assess the kinetic release of the formulation, it was subjected to the following kinetic release models. The parameters R^2 (regression coefficient) were determined by various equations to understand the probable release mechanism.

TASTE MASKING EVALUATION

By Panel testing

The panel testing is a psychophysical rating of the gustatory stimuli. The test was performed with 10 human volunteers. The study protocol was explained and written consent was obtained from volunteers. The sample was evaluated on the bitterness value. The samples were held in the mouth for different time intervals (10sec, 1min and 2min) and the evaluated on the bitterness scale.

Score	Inference
0	Pleasant
1	Tasteless
2	Slightly bitter
3	Moderately bitter
4	Extremely bitter

STABILITY STUDIES

The accelerated stability studies were carried out by keeping the optimized batch at room temperature and humidity condition and 40 ± 2^{0}C / 75 ±5% RH in stability chambers for a period of 6 months. The tablets were checked for all the physical parameters, content uniformity and in vitro dissolution. The tablet was kept wrapped in aluminum foil depicting strip packing. The drug content evaluation was carried out using HPLC to detect the presence of any impurity if formed.

RESULTS

Preformulation details of the drug and is compatibility profile:

- Excipient compatibility

IR spectrum of Cefpodoxime Proxetil showed all the peaks corresponding to the functional group present in the structure of Cefpodoxime proxetil. Figure.1. shows the FTIR data of the drug and the polymer which states the excipient compatibility.

The possible interaction between the drug and the polymers was studied by IR Spectroscopy. The IR spectrum's of Pure Drug, Physical mixture of Cefpodoxime Proxetil with HPMC K15M and Ethyl cellulose, the final physical blend of the formulation and the Minitablets. The spectra was taken on 0 day and again on 30 day after storing the samples in accelerated storage condition of 40^0C and 75% RH.

The results revealed no considerable changes in the IR peaks of Cefpodoxime Proxetil.

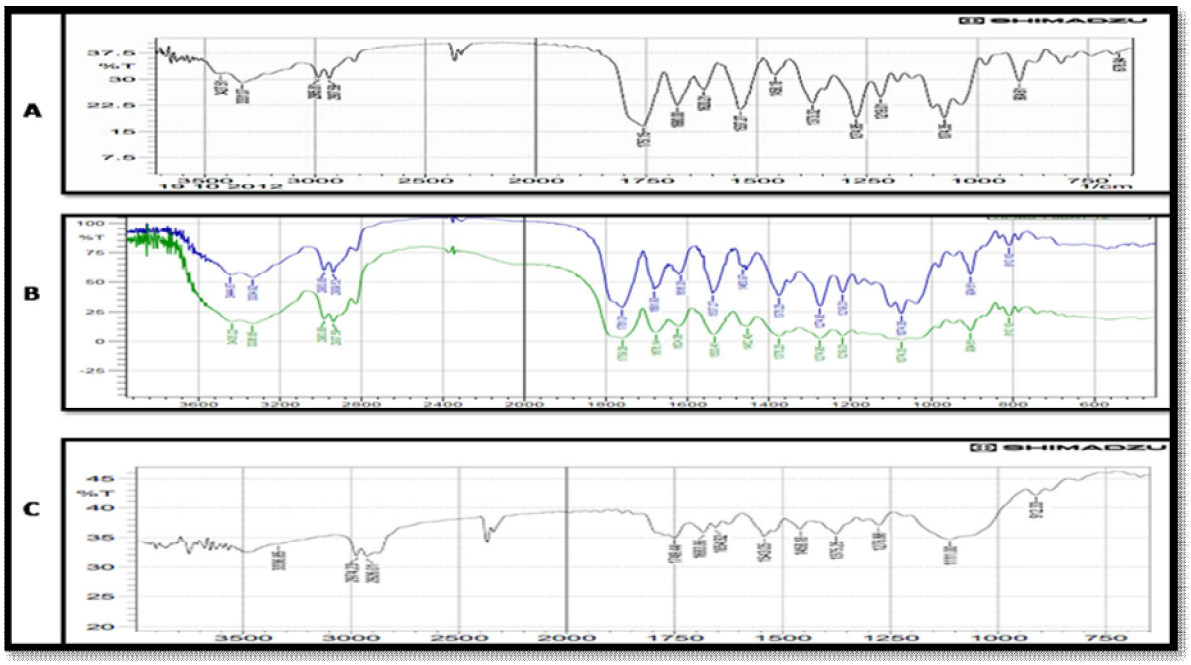

Figure.1: Excipient compatibility using FTRI: (A) Spectra of pure drug, (B) Spectra of drug with HPMC K15 M at 0 day and after 30 days (C) Spectra of final Minitablet formulation.

- Calibration curve using UV spectroscopy

Spectrum of Cefpodoxime Proxetil was obtained and wavelength maxima (λ max) were obtained to be 263nm in pH1.2 buffer. The concentration range of 1-25 ppm was selected for development of standard curve in the different Medias. At the above λ max of 263nm a linear curve was obtained (n=3) and correlation regression value was obtained.

The equation obtained was y = 0.033x - 0.001 with an R^2 value of 0.9999.

EVALUATION OF THE ODMT

The different batches of the orally dispersible Minitablets were prepared by varying the concentration of the superdisintegrants. All the batches were evaluated to check the basic tablet properties like hardness, friability.etc. and the dispersion time. Good dispersion was obtained using 0.5% Crosscarmellose sodium.

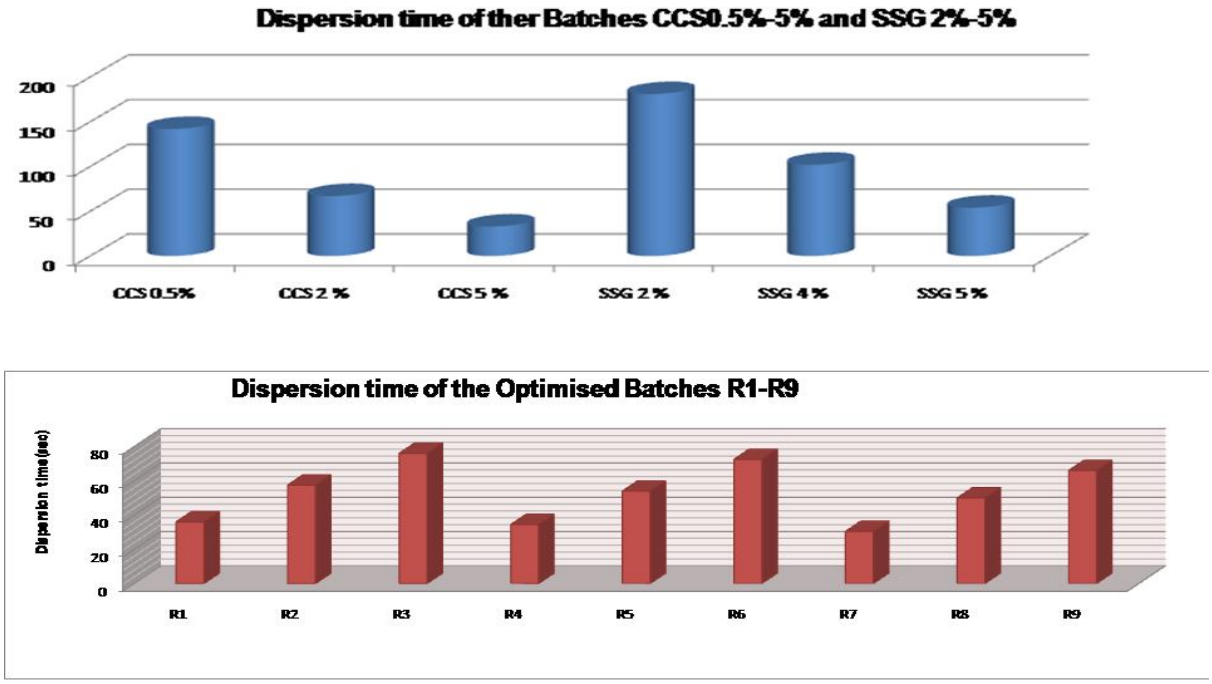

Figure 2: The dispersion time comparision of the different Minitablet batches.

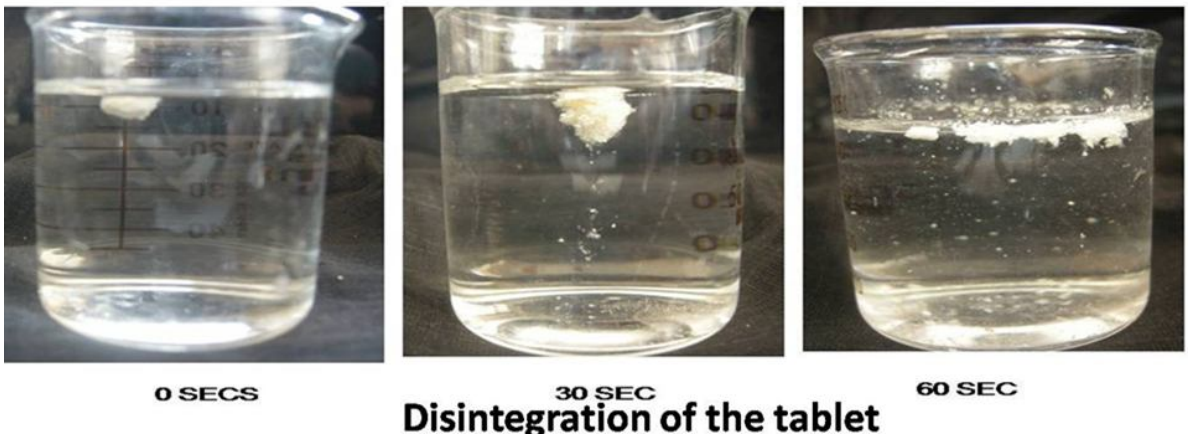

Figure 3: Dispersion of Minitablet over a period of 60 secFinal Equation in Terms of Coded Factors of Dispersion time:

Disintegration time = +54.22 -3.83 * X_1 +19.00 * X_2 -1.00 * X_1 * X_2 -0.83 * X_1^2 -1.33* X_2^2

In this case both the factors X_1 (i.e. Concentration of Crosscarmellose Sodium) and X_2 (i.e. Hardness) are a significant model terms which significantly affect the Dispersion time of the Minitablets. It is also indicated by the Prob > F value of X_1^2 i.e. 0.0002 and X_2^2 i.e. <0.0001.

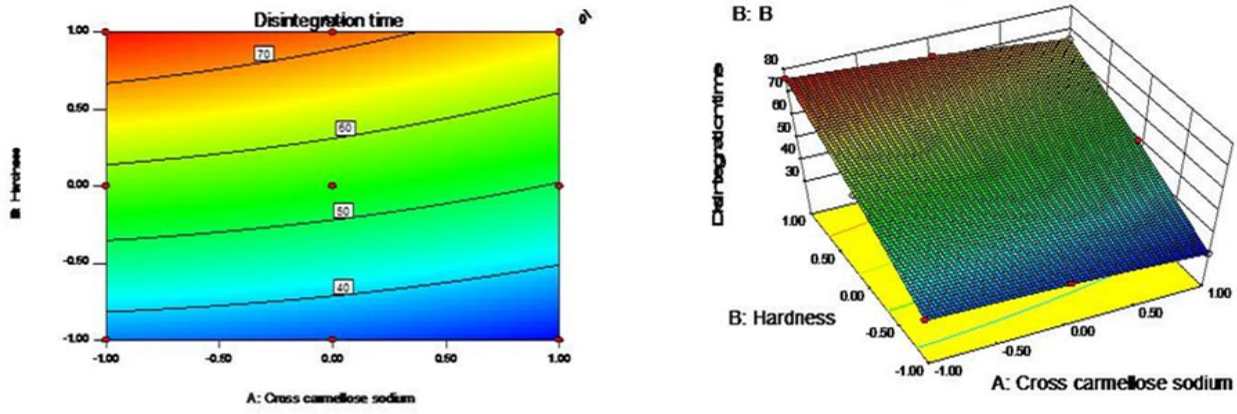

Figure.4: Factorial design Counter plot and 3-D surface plot of the different optimization batches.

The 3-D Responce Surface plot shows that an the highest dispersion time is obtained with an lower Concentartion of Crosscarmellose sodium and at high Hardness. From the equation it is seen that by increasing the concentration of Crosscarmellose sodium the dispersion time of the minitablet can be reduced as required. Also the dispersion time of the formulation can be reduced by reducing the hardness of the tablet. The coefficient of the concentration of Crosscarmellose sodium is 'negative' thus increasing the concnentration of crosscarmellose sodium the dispersion time of the tablet can be reduced. The coefficient of hardness factor if 'positive' so by decreasing the hardness the dispersion time of the tablet can reduced.

All the optimization batches of the Minitablets were subjected to the basic evalaution parameters. The parameters of the different bacthseba re given in the Table. 2. A comparision of all the data of dissolution profile of the formulation is shown in Figure 5.

Table.2: Batches for the Optimization of Dispersion Time of Minitablets:

Parameter	J1	J2	J3	J4	J5	J6	J7	J8	J9	CPOM
Thickness (mm)	4.07± 0.1	3.99± 0.07	4.11± 0.04	4.03± 0.1	4.0± 0.07	4.07± 0.04	4.11± 0.05	3.98± 0.1	4.07± 0.06	4.2 ± 0.05
Hardness (kg/cm^3)	2±0.2	3±0.4	4±0.2	2±0.4	3±0.2	4±1.0	2±0.2	3±0.4	4±0.4	3.0 ± 0.2
Content uniformity (%)	100.4 ±0.11	99.7± 0.13	101.4 ±0.15	101.5± 0.14	100.7 ±0.15	99.4± 0.14	99.8± 0.12	102.4 ±0.12	101.7 ±0.14	99.8 ± 1.3

Wetting time (sec)	10± 2.1	10±.0	9± 2.1	6± 1.0	7± 1.0	8± 2.0	8± 2.2	6± 1.7	6± 1.7	7.4 ± 1.5
Water absorption ratio	171	154	107	192	144	127	218	174	133	117.82
Friability	0.77± 0.01	0.77± 0.14	0.74± 0.07	0.81±0 .04	0.79± 0.11	0.77± 0.07	0.79± 0.07	0.80± 0.11	0.77± 0.14	0.73 ± 0.01
Dispersion time (sec)	**36± 2**	**57.5 ±3**	**76 ± 3**	**34.5 ±2**	**54± 3**	**72.5 ±3**	**30. 5 ±4**	**50± 3**	**66± 3**	68 ± 1.0

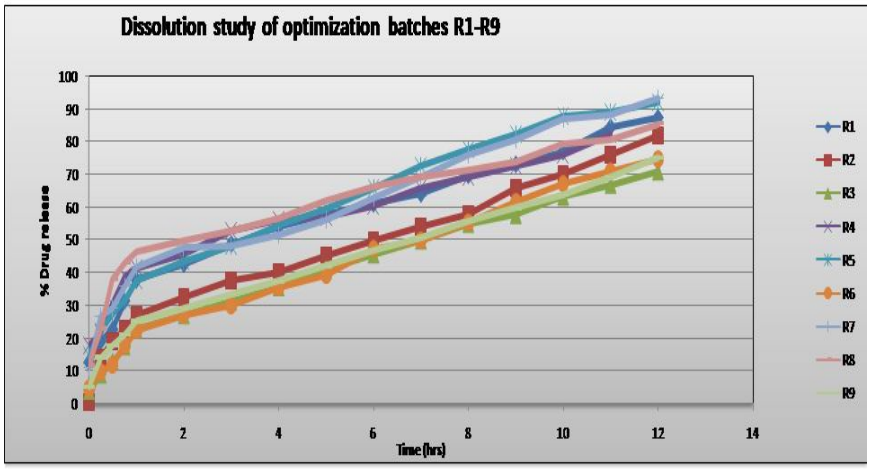

Figure 5: Dissolution study profile of the Optimization batch of the Minitablets.

KINETIC MODELLING OF THE DRUG

After studying the drug release profile of all the batches the optimized batches were subjected to kinetic modeling to determine the drug release mechanism. The regression coefficient and the equation of the batches are given in the Table. 3.

The drug release follows **Korsmeyer-Peppas** release mechanism as the regression coefficient is found to be very close to1. The release exponent of the profile is the slope of the straight line. Thus from the above equation we can calculate the value of 'n'; which was found to be less than 0.45 for both the optimized Minitablets. We can thus conclude that the formulation follows Fickian diffusion for the drug release.

Table.3: Kinetic modelling of the Optimized batches of Microspheres and Minitablets.

Batch	**Minitablets 'CPOM'**		**Marketed formulation**	
	R^2	**Equation**	**R^2**	**Equation**
Zero order	0.963	y = 6.618x + 19.39	0.953	y = 26.68x + 30.05
First order	0.87	y = 0.064x + 1.365	0.88	y = 0.172x + 1.556
Higuchi matrix system	0.951	y = 0.240x + 1.188	0.956	y = 0.410x + 1.345

Korsmeyer-Peppas	0.987	y = 0.411x + 1.461	0.983	y = 0.485x + 1.791
Hixxon Crowell model	0.898	y = -0.163x + 1.860	0.914	y = -0.578x + 1.479

TASTE MASKING EVALUATION OF THE OPTIMISED BATCHES OF THE FORMULATION

The different samples Minitablets was evaluated using the Bitterness scale. All the volunteers gave a score of **4** for the plain drug while the coated drug particles scored **1** signifying that they are tasteless while the Minitablets got a score of **0** which state that they have a pleasant taste. The detailed results are given in Table 4.

Table 4: Evaluation of the taste masking of the drug using Panel testing:

Volunteers	Time (sec)	Batches				
		1	**2**	**3**	**4**	**5**
1	**10**	4	1	1	1	0
	60	-	1	1	1	0
	120	-	1	2	1	1
2	**10**	4	1	1	1	0
	60	-	1	1	1	0
	120	-	1	1	1	0
3	**10**	4	1	1	1	0
	60	-	1	1	1	0
	120	-	1	2	1	0
4	**10**	4	1	1	1	0
	60	-	1	1	1	0
	120	-	1	1	1	1
5	**10**	4	1	1	1	0
	60	-	1	1	1	0
	120	-	1	1	1	0
6	**10**	4	1	1	1	0
	60	-	1	1	1	0
	120	-	1	1	1	0
7	**10**	4	1	1	1	0
	60	-	1	1	1	0
	120	-	1	1	1	2
8	**10**	4	1	1	1	0
	60	-	1	1	1	0
	120	-	1	1	1	0
9	**10**	4	1	1	1	0
	60	-	1	1	1	0
	120	-	1	2	1	1
10	**10**	4	1	1	1	0
	60	-	1	1	1	0
	120	-	1	1	1	0

STABILITY STUDIES

The stability of the samples was carried out at 40 ± 2^0C/ 75 ± 5% RH. The samples were evaluated at intervals of 0day, 15days, 30days, 60days, 90days and 180days. The different evaluation parameters are given in the Table.5.

Table.5: Stability data of the optimized batches

Parameter	0day	15days	30days	60days	90days	180days
Average weight (mg)	99.8 ± 1.3	100.2 ± 1.3	100.3 ± 1.5	98.9 ±1.4	100.1 ± 1.3	99.4 ± 1.4
Thickness (mm)	4.2 ± 0.05	4.24 ±0.1	4.18 ± 0.05	4.22 ± 0.05	4.21 ±0.1	4.22 ± 0.1
Hardness (kg/cm^2)	3.0 ± 0.02	3.8 ± 0.04	2.8 ± 0.02	3.0 ± 0.04	3.2 ± 0.04	3.0 ± 0.04
Friability (%w/w)	0.73 ± 0.01	0.79 ± 0.02	0.74 ± 0.11	0.78 ± 0.07	0.74 ± 0.09	0.75 ± 0.11
Disintegration time (sec)	68.66 ± 1.5	64.2 ± 1.24	65.34 ± 1.54	67.4 ± 1.34	68.45 ± 1.56	67.63 ± 1.43
% Buoyancy after 12hrs.	75.52 ± 1.0	78.33 ± 0.94	72.39 ± 0.48	77.41 ± 0.62	75.19 ± 0.81	76.38 ± 1.02
Drug content	102.3 ± 0.2	99.92± 0.27	99.89 ± 0.21	99.35 ± 0.38	99.21 ± 0.3	98.32 ± 0.25
Drug release after 12hrs	93.2±0.88	92.69± 0.1	93.2±0.18	93.21±0.17	93.4±0.188	93.58±0.542

Drug content determination of the stability batches

HPLC

The drug content of the stability batches were evaluated using HPLC. This gave a better idea about the drug content over the entire period. It will be also help to detect the peaks of any possible degraded API. The HPLC used was Agilent 1200 series having the Chemstation software. Cefpodoxime Proxetil has two epimeric active forms 1.e. R epimer and S epimer. Resolution factor R between the cefpodoxime proxetil S and R epimer peaks, and tailing factor t were calculated. The chromatogram of the drug, the linearity curve using HPLC and the stability study chromatogram of 0 day and 6 months are shown in the Figure.6.

Parameters of HPLC

Parameters	Specification
λmax	261nm
Flow	1 ml/min
Temperature	Not defined
Column	Zorbax Eclipse® XDB- C18, Analytical 4.6 x 150mm, 5µm column

Mobile phase Methanol : Water (55:45)

The concentration curve of the drug was drawn and the equation obtained was

Y = 25.54x + 11.06 with the regression coefficient value (R^2) of 0.999.

From the stability study data we can conclude that the formulation is stable during the period of the study.

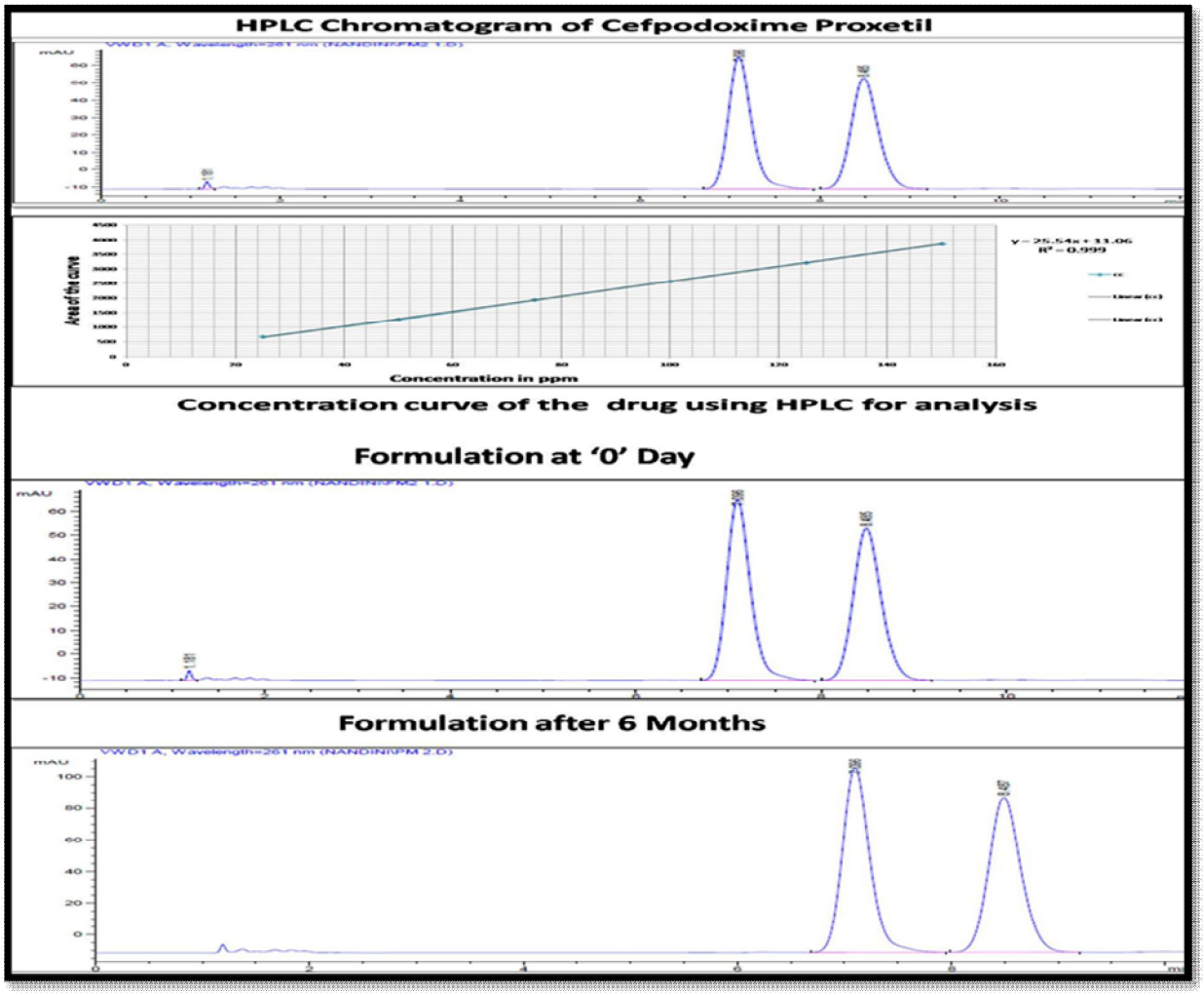

Figure 6: HPLC chromatogram of the drug.

CONCLUSION

The drug Cefpodoxime Proxetil was successfully coated with the polymer HPMC K15M and Ethyl cellulose using solvent evaporation technique. These coated particles were further used for the study to formulate and optimize the orally dispersible Minitablets. The Minitablets were factorial design to get the desired dispersion time. The Orally dispersible Minitablet batches were evaluated for Hardness, Friability, Drug release and Dispersion time.

The optimized batch of the Minitablets was subjected to taste masking evaluation with a panel of 10 human volunteers. Sufficient taste masking was observed. The sufficient taste masking was observed with both the batches. It was also seen that the batches gave desired in vitro drug result after 12hrs study using USP Dissolution type II apparatus. Also the batches were found to be stable for a period of 6 months at 45^0C / 75% RH. The drug content of the stability was conducted using HPLC to detect the formation of any degradent during the 6months duration.

Thus it was found that the Cefpodoxime Proxetil coated with sustained release polymers like HPMC K15M and Ethyl cellulose and then compressed into Orally dispersible Minitablet can be used as a Potential Drug Delivery system for the Paediatrics with common infections like Otitis media etc.

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