DESIGN AND INVESTIGATION OF ORALLY FAST DISINTEGRATING TABLETS OF AMOXCILLIN MICROSPHERES FOR SUSTAINED RELEASE IN PEADIATRIC POPULATION

Krithi Nanaiah A[1*], Dr Marina Koland[2]

1*-Department of Pharmaceutics, Nargund College of Pharmacy,Bengaluru

2 – Department of Pharmaceutics , Nitte Gulabi Shetty Memorial Institute of Pharmaceutical Sciences, Mangalore

Author for Correspondence

Krithi Nanaiah A
Asst Prof
Nargund College of Pharmacy
Banshankari 3rd stage
Bengaluru-85

ABSTRACT

Amoxicillin Trihydrate is a ß-lactam antibiotics used to treat bacterial infection. It is one of the most common antibiotics prescribed for children, but therapy suffers from low patient's compliances due to unpleasant taste. This study was aimed to develop taste masked microspheres of amoxicillin using Eudragit RSPO and Ethyl cellulose then prepared oral fast disintegrating tablets from formulated microspheres using super disintegrants for paediatric dosage form. Solvent evaporation method was used to prepare microspheres. The prepared microspheres were subjected to various evaluation and *in-vitro* release studies. Through optical microscopy and SEM analysis particle size of the microspheres were determined. The prepared microspheres had good spherical geometry with smooth surface as evidence of SEM. The tablets were prepared using different concentration of disintegrant by direct compression method. The super disintegrants used in this study were Sodium starch glycolate (SSG),

Croscarmellose Sodium (CCS). The formulated tablets were evaluated for uniformity of weight, thickness, hardness, friability, wetting time, water absorption ratio, disintegration time and dissolution study. From the in-vitro drug release profile and taste evaluation it was concluded that G1, G3, G4, K1, K3 and K4 were the optimal formulations for sustain release and palatability of the drug**.** The stability studies conducted showed that there was no appreciable change when stored at refrigeration temperature 2-8°C, room temperature 25-30°C and oven temperature 45-50°C.The results obtained from the study suggested the use of Eudragit and Ethyl cellulose polymer for preparing amoxicillin loaded microspheres with an aim to mask the bitter taste of the drug and furthermore oral fast disintegrating tablet could be formulated for better patient compliance, dose accuracy and improve stability.

KEYWORDS: Amoxicillin, Microspheres, Oral fast disintegrating tablet.

Introduction

Oral route is the most preferred route for administration of various drugs because it is regarded as most convenient and economical route particularly for children.

Very little work has been done for development of pediatric dosage form which is relevant to sustain release also. Commonly employed dosage form by oral routes includes tablets, capsules, suspensions and liquids in pediatrics. But drug may be less stable in liquid formulation rather than in tablets or capsules. Most children below the age of ten years find it difficult to swallow tablets or capsules intact. The tablet form is unsuitable for drugs that taste bitter and possess an unpleasant odour.

Particularly in an antibiotic therapy where dose and duration of therapy is important, patient compliance plays significant role in completing the course and thereby achieving required antibiotic concentration. Pediatric patient compliance is better for the drugs that have nice taste and can be administered easily. Accordingly, it is important to mask the unpalatable taste of a drug, such as antibiotics in order to improve the patient compliance and successful completion of therapy.

From the various techniques available microspheres or microcapsules are prepared which are capable of masking the unpleasant taste and prolonging drug release are then incorporated into suspensions or compressed into rapidly disintegrating tablets. Suspension has the disadvantage of poor stability and

less dose accuracy. Hence in the present study rapidly disintegrating tablets were prepared using amoxcillin microspheres with super disintegrates which are commonly used as far as taste masking is concerned by incorporating various flavoring and sweetening agents. Moreover the polymers used provide protection to the active moiety which increases its stability [1,2,3,4]. Hence, provided preferred dosage form for the drugs having short half-life, so as to maintain the drug plasma level in therapeutic index for prolonged period of time[5]

MATERIALS:

Amoxcillin and Aspartame was obtained from Yarrow Chem Pdt., Ethyl Cellulose , Eudragit RS 100, Tween 80, Sodium chloride was obtained from Himedia., Magnesium sterate, Carboxy Methyl cellulose (sodium salt), Talc, Vanillin, Potassium dihydrogen orthophosphate, Petroleum ether and Sodium starch glycolate was obtained from Loba Chemie., Paraffin liquid(light), n-Hexane, Aerosil from CDH., Cellulose microcrystalline from Thomas Baker, D-mannitol from Rankem., Chloroform, Acetone, Hydrochloric acid from Merck., Disodium hydrogen orthophosphate from NICE.

PREPARATION OF MICROSPHERES CONTAINING AMOXICILLIN

Microsphere containing amoxicillin were prepared by solvent evaporation method. Drug loaded microspheres were prepared using two different polymers (i.e. Ethyl Cellulose and Eudragit RS 100). Drug and polymer different ratios were taken and dissolved with solvents and co-solvents at room temperature and stirred for 3 hours. Here 200 ml of sodium CMC (0.5%) containing (1%v/v) tween 80 were used as co-solvents along with chloroform as a solvent for Ethyl Cellulose polymer and 100ml of liquid paraffin containing 1% w/w of span 80 were used as co-solvents along with acetone as a solvent for Eudragit RS100 polymer as shown in Table No 1 Both the microspheres were collected by decantation and the product was washed thoroughly with petroleum ether (40-60ºC), four times and dried at room temperature for 3 hours, then stored in a desiccator over fused calcium chloride.

Table No 1: Formulation of Microspheres

Formulation code	Amount of drug	Amount of polymer	Amount of solvent
EC-1	1g	1g	100ml
EC-2	1g	2g	100ml

EC-3	2g	1g	100ml
EU-1	1g	1g	40ml
EU-2	1g	2g	40ml
EU-3	2g	1g	40ml

Percentage Yield:

The dried microspheres were weighted and percentage yield of microspheres were calculated by using the formula,

$$\% \text{ Yield} = \frac{Weight\ of\ Microspheres}{Weigh\ \ of\ Polymer+Drug} \ x\ 100$$

Drug Content :

The various batches of the microspheres were subjected for drug content analysis by accurately weighing microspheres samples which is mechanically powdered. The samples were dissolved in adequate quantity of 0.1N HCl then filtered. The UV absorbance of the filtrate was measured using a UV spectrometer at 228nm.

Drug Encapsulation efficiency:

Drug loading and encapsulation efficiency was determined for all batches using the formula and values were expressed as percentage.

$$\text{Encapsulation efficiency} = \frac{Practical\ drug\ content}{Theroetica\ \ Drug\ Content} \ x\ 100$$

Particle Size Analysis:

Size distribution plays a very important role in determining the release characteristics of the microspheres. Particle size distribution analysis was done by optical microscopy method using calibrated eye piece micrometer nearly 100 particles were measured and the results were determined.

Scanning Electron Microscopy (SEM) for shape and surface characterization:

SEM was used to determine particle size distribution, surface topography, texture and also to examine the morphology of fractured and sectioned surface. The microspheres were fixed on brass stub with an adhesive and sputter coated with platinum at 20mA current for 90 seconds of auto-fine coater. Samples were then scanned using vacuum at an accelerating voltage of 1 kV. SEM is probably the most commonly used methods for characterizing drug delivery systems, owing in large part to simplicity of sample preparation and ease of operation.

IR Spectra of a pure drug:

The IR spectrum of pure drug was found to be similar to the standard spectrum of Amoxicillin trihydrate. The spectrum of Amoxicillin trihydrate shows the following functional groups at their frequencies: 1775cm^{-1} (O-H stretch), 1583cm^{-1} (C-H stretch), 1684^{-1}, 1248cm^{-1}, (C=O stretch). The other principle peaks were 1613cm^{-1} and 1313cm^{-1} respectively.

***In-vitro* drug release:**

The USP XXIV dissolution rate testing apparatus was employed to study the release of amoxicillin. 900 ml of buffer in simulated gastrointestinal pH conditions, viz, simulated gastric fluid (0.1N HCl, pH 1.2) for the first 2hr. followed by 6hrs in simulated intestinal fluid (phosphate buffer solution, PBS, pH 6.8).Dissolution test was being carried out at 50 rpm maintained at 37ºC±0.5ºC. 5ml of sample were withdrawn at specific time interval for 8hrs. The withdrawn samples were diluted; if necessary. The sample volume was replaced by an equal volume of fresh medium. The concentration was determined spectrophotometrically at 228nm. The same procedure was repeated for other formulations also. The percentage of drug release at various time intervals was calculated and plotted against time[6,7].

Preparation of tablets containing amoxicillin microspheres

Accurately weight microsphere (250mg), super-disintegrants all other excipients and additives were passed through #60 sieves prior to mixing. The microspheres was properly mixed with disintegrants, and then with diluent mannitol. The mixture was mixed with aspartame, talc, magnesium stearate, aerosil and vanillin as shown in Table No 2. The direct compressible mixtures were compressed using Single Press Rotary Machine (MINIPRESS) with a compression force of 6.5 tonnes. Shape: Flat, bevel edges on both sides. Sizes of punches: 8.0 mm round [8,9].

Table No 2 : Formulation of Orally Fast Disintegrating Tablets of Amoxicillin Microsphere

Ingredients (mg/tab)	**Formulation Code**											
	G1	**G2**	**G3**	**G4**	**G5**	**G6**	**K1**	**K2**	**K3**	**K4**	**K5**	**K6**
Amoxicillin microspheres	250	250	250	250	250	250	250	250	250	250	250	250
Croscarmellose Sodium(CCS)	44	44	44	44	44	44	-	-	-	-	-	-

Sodium starch Glycolate(SSG)	-	-	-	-	-	-	44	44	44	44	44	44
Aspartame	10	-	28	10	28	-	10	-	28	10	28	-
Mannitol	40	80	-	40	-	80	40	80	-	40	-	80
Avicel(MCC)	73	73	73	73	73	73	73	73	73	73	73	73
Magnesium stearate	6	6	6	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6	6	6	6
Aerosil	6	6	6	6	6	6	6	6	6	6	6	6
Flavor (vanillin)	7	7	7	7	7	7	7	7	7	7	7	7

Evaluation of tablets :

The thickness of the tablet was determined by using Vernier caliper. The hardness of the tablet by Monsanto hardness tester and it was found to be in the limited range of 4-6 kg/cm^2 .Uniformity of weight was also determined as per Indian Pharmacopoeia. As per USP, friability was done using Roche Friabilator. Percentage friability of all formulations was in the range of 0.28 to 0.33 % which was below 1%, indicating that friability is withinthe prescribed limits.

Drug content uniformity:

Random tablets were taken and crushed, added 50ml of 0.1N HCl.Shaken for 30 mins and added sufficient amount of 0.1N HCl to make-up the volume upto 100ml and then filtered. From this solution 1ml was added to another 100ml volumetric flask and made up the volume upto the mark.Then the absorbance spectrophotometrically at 228nm [10]

***In vitro* dispersible time (with simulated salivary fluid):**

The test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as an oro-dispersible tablet.*In vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of simulated salivary fluid of pH 6.8.Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

***In vitro* dissolution studies:**

The USP XXIII dissolution rate testing apparatus was employed to study the release of amoxicillin. 900 ml of buffer in simulated gastrointestinal pHconditions, via, simulated gastric fluid (0.1M HCl, pH 1.2) for the first 2 hr. followed by 6 hr in simulated intestinal fluid (phosphate buffer solution, PBS, pH 6.8).Dissolution test was being carried out at 50 rpm maintained at 37ºC±0.5ºC.

5ml of sample were withdrawn at specific time interval for 8hours. The withdrawn samples were diluted; if necessary. The sample volume was replaced by an equal volume of fresh medium. The concentration was determinedspectro-photometrically at 228nm. The same procedure was repeated for other formulations also. The percentage of drug release at various time intervals was calculated and plotted against time[11].

***In-vivo* disintegration test**

In this study taste evaluation and *in-vivo* disintegration test was conducted on healthy volunteers. Approval was granted by "Central Ethics Committee" NitteUniversity (Ref: NU/CEC/P.G.-37/2012)

Taste evaluation testPanel Tasting:

Taste evaluation was done by a panel tasting. In this method 5-10 human volunteers were trained for taste evaluation by using standard tablet(i.e. tablets prepared without any sweeteners and flavours). Volunteers were asked to taste the rate it in scale of taste quality and intensity. After the test they were asked to rinse out their mouth with deionized water. Salty crackers were provided to neutralize the taste after tasting standard tablets each of all formulations (i.e. tablets prepared with different combination of sweeteners and flavours). Subsequently test tablets will also be rated numerically based onthe levels of bitterness.(e.g. 0-5) where 0 was rated as pleasant with no bitterness while 5 was rated unbearable bitter.

***In vivo* disintegration time:**

Six healthy human volunteers were selected and their written consent was obtained. Each volunteer randomly took one Placebo tablet (tablet without drug) and kept on the tongue. The time taken for complete disintegration ofthe tablet on the tongue was noted. It is expressed in seconds. After the test, mouth was washed with distilled water. 3 trials were performed with 2 days interval, between trials[12]

In both the batches, formulations 1, 3 and 4 showed an excellent taste masking effect due to the effect of sweeteners and flavour in different ratio and also dissolved in mouth easily in a required period of time of 29 to 42 sec. Thus these formulations fulfill the requirement of Fast Disintegrating Tablet.

Results and Discussion

The percentage yield of microspheres, drug content and entrapment efficiency was done as per the methods describe in methodology and result are discuss in the given table below. The encapsulation efficiency of all formulations was high and Eudragit RSPO led to high encapsulation efficiency compared to Ethyl cellulose microspheres, which might be related to a faster precipitation of Eudragit RSPO in the continuous phase than ethyl cellulose.

Table 3: Percentage yield, Drug Content and Entrapment efficiency of microsphere formulation

Formulation	% Yield	Mean particle size (µm)	Drug Content(%)	Drug entrapment Efficiency
EC-1	94.8	224.64	73.23	81.82
EC-2	84.16	361.71	63.70	75.34
EC-3	98.56	349.16	84.36	91.4
EU-1	92.85	316.33	85.03	91.28
EU-2	78.16	455.12	78.11	86.63
EU-3	90.1	301.24	72.13	80.72

The mean particle size was measured to be in between 224.64 to 455.12 **µm.** Particle size analysis of the microspheres showed that the mean particle size was affected by variation in the drug to polymer ratio. The increase in mean particle size with increase in polymer concentration may have occurred due to the significant increase in the viscosity in a fixed volume of solvent.

The formulated microspheres of Eudragit RSPO was found to be more spherical and surface was found smooth compared to the Ethyl cellulose Microspheres.

Fig 1: SEM of Microspheres loaded with amoxicillin

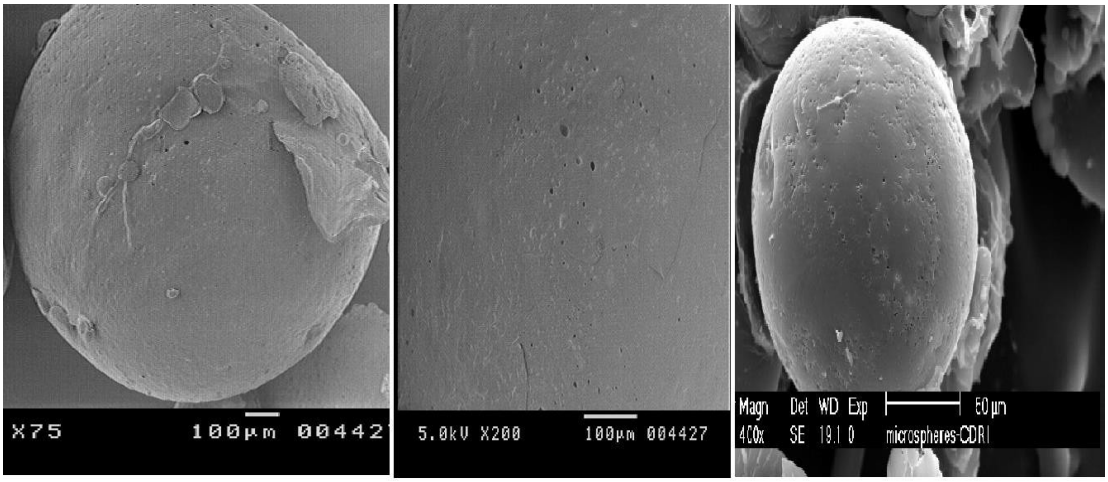
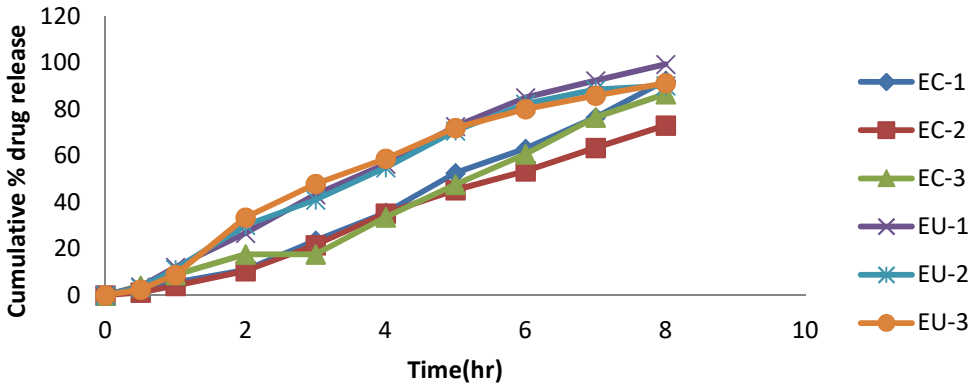


Table 4: Cumalative % Drug Release for microspheres

pH	Time (hr)	Cumulative % drug released*					
		EC-1	**EC-2**	**EC-3**	**EU-1**	**EU-2**	**EU-3**
0.1 HCl buffer	0	0	0	0	0	0	0
	0.5	2.09	1.25	4.18	3.76	3.34	2.51

	1	5.44	4.18	8.79	12.13	11.30	8.79
	2	10.88	10.4	17.58	26.7	30.13	33.4
6.8 Salivar phosphate buffer	3	23.56	21.63	17.58	43.26	40.94	47.89
	4	35.53	35.15	33.60	56.39	54.84	58.71
	5	52.53	45.19	47.51	72.61	70.68	71.84
	6	62.96	53.30	60.64	84.97	82.27	79.95
	7	76.48	63.34	76.48	92.31	88.45	85.75
	8	92.31	73.00	86.52	99.27	90	91.15

Fig 2:Cumulative % Drug Release for Microspheres



The pre-compression parameters study of granules reflected that the granules were having satisfactory flow properties. The result are shown in table 5

Table 5: Powder flow properties

Formulation	Bulk density*	Tapped density*	Carr's Index*	Hausner 's Ratio*	Angle of repose*
EC-1	0.379	0.4433	14.042	1.169	20.1º
EC-2	0.368	0.4427	15.67	1.186	22.7º
EC-3	0.371	0.4437	16.1	1.192	20.9º
EU-1	0.368	0.4427	11.44	1.129	21.3º
EU-2	0.370	0.4313	14.68	1.172	23.7º
EU-3	0.376	0.4430	17.44	1.178	22.3º

*Average of three readings

The best formulations for tablet were selected based on their taste. The tablets were formulated using two different super disintegranting agents i.e. Croscarmellose Sodium and Sodium Starch Glycolate, which were coded as G and K respectively. Further evaluations of a compressed tablet were done based on these tests and all the tablets general apperance of both the formulations where evaluated and found to be ideal white colour with flat and bevel shape and vanillin odour.

Table 6 : Physical properties of the tablet formulation

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Drug Content (%)	Weight Variation (%)	Friability (%)	*InVitro* Dispers-ible Time(sec)	*In-Vivo* Disintegra-tion Time (sec)
G1	2.07	3.4	95.21	3.8	0.30	38	30
G2	2.08	3.5	70.63	3.3	0.33	37	41
G3	2.05	3.7	95.98	3.1	0.31	36	32
G4	2.09	3.5	97.01	4.2	0.31	29	30
G5	2.07	3.8	80.11	4.0	0.30	40	35
G6	2.09	3.7	75.13	3.8	0.32	37	40
K1	2.07	3.1	94.36	3.9	0.29	28	29
K2	2.06	3.4	71	3.9	0.31	38	40
K3	2.03	3.2	96.53	3.6	0.30	31	30
K4	2.09	3.1	98.23	3.2	0.28	29	28
K5	2.07	3.7	82.13	3.9	0.33	30	33
K6	2.05	3.6	77.9	3.3	0.33	37	39

The hardness of the tablet by Monsanto hardness tester and it was found to be in the limited range of 4-6 kg/cm^2 Percentage friability of all formulations was in the range of 0.28 to 0.33 % which was below 1%, indicating that friability is withinthe prescribed limits.

To be compliant with IP standards, tablet should disintegrate within 60 seconds . But formulated products of both batches have exhibited very less disintegrating time of 27 to 40 seconds, indicating that they are suitable as oral fast disintegrating tablets. The *in-vivo* disintegrating time found to bein

the range of 28 to 42 sec respectively. While *in-vitro* dispersible time was found to be in the range of 28 to 44 sec. The above results indicate that the tablets were suitable for fast disintegrating tablet as shown in Table 6.

Table 7 : Dissolution study profile of formulation of tablet G1-G6

pH	Time (hr)	Cumulative % drug released*					
		G1	G2	G3	G4	G5	G6
0.1N HCl buffer	0	0	0	0	0	0	0
	0.5	1.67	1.67	0.41	3.76	3.34	2.93
	1	5.44	5.02	7.95	12.13	12.55	9.62
	2	10.04	11.30	16.74	26.79	31.39	34.74
6.8 Salivary phosphate buffer	3	23.94	21.63	32.83	42.48	41.33	48.28
	4	36.30	35.15	47.51	55.23	56.00	59.09
	5	53.69	45.19	61.41	71.45	72.23	72.61
	6	64.12	53.30	76.48	84.20	83.04	80.34
	7	77.25	63.34	86.90	88.84	88.84	86.52
	8	93.09	73.00	97.72	98.49	90.38	91.54

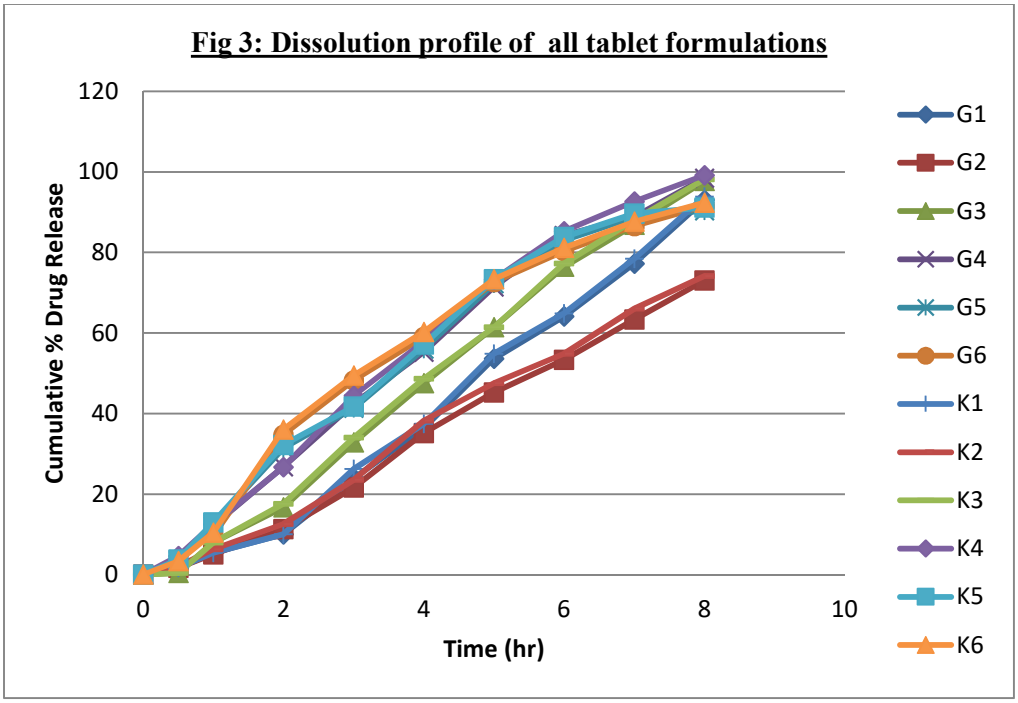
Table 8: Dissolution study profile of formulation of tablet K1-K6

pH	Time (hr)	Cumulative % drug released*					
		K1	K2	K3	K4	K5	K6
0.1N HCl buffer	0	0	0	0	0	0	0
	0.5	1.67	2.09	0.41	4.6	3.76	3.34
	1	5.44	6.27	7.95	12.5	12.97	10.4
	2	10.04	12.55	17.58	26.7	32.23	36
6.8	3	26.26	23.56	33.99	44.4	41.71	49.44
	4	37.46	38.24	48.66	57.9	57.16	60.25

Salivary phosphate buffer	5	54.84	47.51	61.41	73.3	73.39	73.39
	6	64.89	54.84	77.25	85.3	83.81	81.11
	7	78.41	66.05	88.06	92.7	89.61	87.68
	8	93.86	74.16	98.11	99.2	91.15	92.31

Drug release profile of both the batches of tablet formulations showed dependence of polymer concentration on the release rate. When compared with percentage release profile of microspheres it was found that there was no significant difference in the release pattern which shows that the excipients used in the tablet formulation didn't show any interaction with the release pattern.

The formulations containing Eudragit microspheres of ratio 1:1 of both batches i.e. G4 and K4 showed release of 98.49 and 99.2% respectively at the end of 8hr. While in case of Ethyl cellulose microspheres of drug: polymer ratio 2:1 in both batches i.e. G3 and K3 showed maximum release rate due to the lesser polymer concentration as compared to rest formulations. Decrease in the percentage release profile was observed due to the increase in the polymer concentration in both the batches of tablet formulation of G2, G5, K2 and K5 in the range of 73, 90.38, 74.16 and 91.15% respectively. The remaining formulation G1, G6, K1 and K6 were found to be 93.09, 91.54, 93.86 and 92.31 % respectively.



Kinetic studies

The R^2 values showed that all the formulations of both the batches of tablet showed zero order release kinetics except G6 and K6 which showed first orderrelease kinetics. The best fitted model for G3, G4 and K3 was found to be zeroorder while for G1, G2, K1, K2 and K4 was found to be first order. G5, G6,K5 and K6 where found best fitted in Hixson and Crowell. From the values of release exponent "n" value obtained that the mechanism of drug release was Non-Fickian super case II where n > 1.0 for all the formulations. Apart from that the R^2 value of Higuchi matrix model for all the formulation stated that they were substantial.

Table 9: Kinetic studies of all tablet formulation

Formulation	Zero Order	First Order	Higuchi Plot	Korsmeyer Peppas		Hixson Crowell
	R^2	R^2	R^2	R^2	n-value	R^2
G1	0.9833	0.8776	0.8729	0.9968	1.4517	0.9305
G2	0.9929	0.9649	0.8999	0.9978	1.3774	0.9785
G3	0.9943	0.8707	0.9050	0.9601	1.7726	0.9442
G4	0.9942	0.8937	0.9416	0.9920	1.1533	0.9684
G5	0.9854	0.9763	0.9492	0.9830	1.1569	0.9907
G6	0.9784	0.9843	0.9545	0.9764	1.2240	0.9967
K1	0.9851	0.8772	0.8772	0.9771	1.4585	0.9316
K2	0.9946	0.9689	0.9077	0.9847	1.2882	0.9810
K3	0.9949	0.8661	0.9076	0.9948	1.7739	0.9438

K4	0.9933	0.8781	0.9438	0.9592	1.1085	0.9672
K5	0.9844	0.9760	0.9507	0.9973	1.1255	0.9908
K6	0.9767	0.9837	0.9571	0.9962	1.1804	0.9970

Stability studies:

20 tablets from each batch were selected at random and were packed aluminum foil packs. 10 tablets from each batch were kept in a desiccator at room temperature and other 10 were kept at room temperature on a shelf (at RH 80%) for one month. The tablets were checked for physical appearance, hardness, weight difference, *in vitro* dispersion time and in vitro drug release profile. Then the results were compared with those obtained immediately after compression. [13].

Conclusion

From the in-vitro drug release profile and taste evaluation it was concludedthat G1, G3, G4, K1, K3 and K4 were the optimal formulations for sustain release and palatability of the drug**.**The results of the studies revealed that the choice of combination of microspheres and orally fast disintegrating tablet may be an effective strategy for the designing and development of antibiotics like amoxicillin for easy, reproducible and effective oral controlled drug delivery in pediatrics. Hence, an effective sustained release drug delivery system and taste masking of drug has been developed for amoxicillin in the form of microspheres compressed into tablets for oral delivery for children. Therefore, our objectives were amplyfulfilled.

Reference

1. Gudsoorkar V.R, Rambhan D. Sustain Release of Drug. The Eastern Pharmacist. 1933; 36(432): 41-43
2. Kristensen HG. Development of Paediatric Medicine: Points to Consider in Pharmaceutical Development. World Health Organisation. 2010; 1-22.
3. Benita S, editor. Microencapsulation. New York: Marcel Dekker Inc.; 1996. p. 35-63.
4. Sompur CK, Doijad RC, Patel SM, Maske AP. An Approach for Development of Oral Sustained Release Suspension. Int J Pharm Bio Sci. 2011; 2(2): 320-329.
5. Bhargava A, Rathore R.P.S., Tanwar Y.S., Gupta S, Bhaduka G. Oral Sustained Release Dosage Form: An Opportunity to Prolong the Release of drug. Int J Pharm PharmSci Res. 2011; 3(4): 685-689
6. Sudhamani T. Preparation and Evalution of Ethyl cellulose microspheres of Ibuprofen for Sustained drug delivery. Int. J. Pharma. Res & Dev.2010; 2(8):119-125.
7. Bhat A, Chowdhary KPR, Shoobharani RH, Narasu L. Formulation and Evaluation of Chloropharmacetical drug delivery of theophylline for Nocturnal Asthma. Int. J. Pharm. & Pharm. Sci. 2011; 3(2):204-208.
8. Sharma V, Singh L, Saxena P, Kumar JA. Formulation and Evaluation of Mouth Dissolve Tablet of Cefixime. Int. Res. J. of Pharm. 2011; 2(5):171-174.
9. Reddy GA, Balaji, Naveen KJ, Rajesh BS, Yedla AC. Formulation and Evaluation of Oral Fast Disintegrating Tablets by using Amlodipine Besylate solid dispersion by direct compression method. Scholar Res. Lib. 2012; 4(2):683-694.
10. Yunxia B, Hisakaza S,Yarinabu Y, Kanumi D, Akinobu O and Kotaro I. Preparation and Evaluation of a Compressed Tablet Rapidly Disintegrating in the Oral cavity. Chem. Pharm Bull. 1966; 44(11):2121-7

11. Indian Pharmacopoeia, Govt. of India, ministry of health and family welfare. New Delhi: The controller of publications; 1996. Appendix 7.112,736.

12. Bi Y, Sunada H, Yonezawa Y, Dayo K, Otsuka A, Lida K. Preparation and Evaluation of a Compressed Tablet Rapidly Disintegrating in Oral cavity. Chem Pharm Bull. 1966; 44(11):2121-2127.

13. Shirwaikar AA, Ramesh A. Fast Disintegrating tablets of Atenolol by Dry granulation Method. Int. J Pharm Sci. 2004; 66(4)422-426.

14. Reddy KR, Mutalik S, Reddy S. Once-daily Sustained Release Matrix Tablets of Nicorandil: Formulation and *In-vitro* Evaluation. AAPS Pharm Sci. Tech. 2003; 4(4); 480-88