International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol. 3, No.2, pp 613-618, April-June 2011

Formulation and Evaluation of Bilayered Tablets of Cefixime trihydrate and Dicloxacillin sodium

G.Vinoth Kumar*, K.Anand babu, C.Ramasamy

Department of pharmaceutics, SRM college of pharmacy, SRM University, Kattankulathur-603203, Kanchipuram district, Tamilnadu., India.

Corres.author: gvino_86@yahoo.co.in
Mobile.No:09942367867

Abstract: The aim of present work was to develop a robust formulation of Bi-layer tablets of Cefixime trihydrate and Dicloxacillin sodium using povidone k-30 as binder. The basic aim of any Bi-layer tablet formulation is to separate physically or chemically incompatible ingredients and to produce repeat action or prolonged action tablet. Cefixime is a cephalosporin antibiotic used to treat infections caused by bacteria such as pneumonia, bronchitis, gonorrhea, and ear, lung, throat, and urinary tract infections. Dicloxacillin is a semi synthetic antibiotic which resists destruction by the enzyme penicillinase. It is used to treat different types of infections caused by bacteria such as bronchitis, pneumonia, etc. A total number of nine formulations have been taken to optimize and develop a robust and stable formulation. Wet granulation process was used for the formulation of both layers and the final film coated tablets were evaluated for the thickness, weight variation, hardness, friability, disintegration time, dissolution study. Among the formulations tablets of formulation -5 was taken as optimized formula due to its higher rate of dissolution and compiled all the other parameters with the official specifications.
Keywords: Cefixime trihydrate and Dicloxacillin sodium, Bi-layered tablets, Povidone K-30, Wetgranulation process.

Introduction:

The Bi-layered tablet is innovative drug delivery system. This is novel type of dosage form for oral administration in which one layer contains sustained release drug Dicloxacillin sodium and another layer contains immediate release drug Cefixime tri hydrate. Combination therapy has various advantages over mono therapy such as problem of dose dependent side effects minimized. A low-dose combination of two different agents reduces the dose-related risk; the addition of one agent may counteract some deleterious effects of the other. Using low dosage of two different agents minimizes the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet and thus dosage of the single component can be reduced.

The term Bi-layered tablets refers to tablet containing subunits that may be either the same or different. Bi-layered tablets allow for designing and modulating the dissolution and release characteristics and they are prepared with one layer of drug for immediate release. Bi-layer tablets are preferred when the release profiles of the drugs are different from one another. While second layer designed to release drug latter, either as second dose or in an extended release manner.[1]

The goal in designing sustained or controlled drug delivery system is, to reduce the frequency of the dosing or to increase effectiveness of drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So controlled release dosage form is a dosage form that release one or more drugs continuously in a pre-determined pattern for a fixed period time, either systemically or to a specified target organ.

Controlled release dosage forms provide a better control of plasma drug levels, less

dosage frequency, less side effects, increased efficacy, and constant delivery.

The two aspects are most important to the drug delivery namely, spatial placement and temporal delivery of drug, spatial placements relates to targeting a drug to specific organ or tissues, while temporal delivery refers to controlling and extending the rate of drug delivery to the target tissue.

Sustained release dosage forms, extends the life of the drug so that people shift from three times a day dosing to the new extended release tablets, taking them just once or twice a day.[2]

This study shows how to formulate the Bi-layered tablets of Cefixime and Dicloxacillin by using povidone k-30 as a binder. Cefixime and Dicloxacillin are carboxylic acid derivative. Cefixime and Dicloxacillin Inhibits bacterial cell wall synthesis by binding to one or more of the penicillin binding proteins (PBPs). It is used to treat infections caused by bacteria such as pneumonia, bronchitis, gonorrhea, and ear, lung, throat, and urinary tract infections[2, 3].

The object of this study was to formulate the Bi-layered tablets of Cefixime and Dicloxacillin using povidone k-30 as binder. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances.[1]

Materials and Methods [8-12]

Cefixime and Dicloxacillin were received as a gift sample from Aurobindo pharma, India. Also Povidone k-30, Maize starch, Hydroxy propyl methyl cellulose K4M and K15M was obtained as a gift sample from Aurobindo pharma, Hyderabad, India. All other materials like microcrystalline cellulose-101, Sodium starch glycolate, cross carmellose sodium,Colloidal silicon dioxide, Magnesium stearate, Lake tartrazine, used was of analytical grade and procured from commercial sources.

Preparation of Bi-layer Tablets:

Cefixime and Dicloxacillin Bi-layer tablets were prepared by wet granulation process according to the formula given in the table-1 and 2. Up to nine formulations are prepared. First Dicloxacillin layer is prepared by sifting the materials shown in table-1, through the sieve separately. Then binding agent is prepared by dissolving Povidone k-30 in specified quantity of Isopropyl alcohol. Load the sifted Dicloxacillin, Hydroxy propyl methyl cellulose K4M, Hydroxy propyl methyl cellulose K15M, microcrystalline cellulose in a rapid mixer granulator. Add the binding agent which is previously prepared. Similarly Cefixime layer is prepared by using microcrystalline cellulose, along with ingredients shown in table-22then the tablets were compressed by using the double-sided tablet press has been specifically designed and developed for the production of quality Bi-layer tablets. Dicloxacillin layer blend is initially pre-compressed with low hardness and Cefixime layer blend is compressed over it, till the desired hardness is achieved. This technology is called Bi-layered technology.[4, 5] Bi-layered tablets are coated using Neocota coating machine using Protec Tab C8. Before tablet preparation the mixture blend of all formulations are subjected to preformulation studies like bulk density, tapped density,compressibility index(%), hausner ratio, angle of repose.[6]

Table No.1- Comparative data of various formulations: Dicloxacillin

S.No	Ingredient (mg)	Trials								
		PF1	PF2	PF3	PF4	PF5	PF6	PF7	PF8	PF9
1	**Dicloxacillin**	543	543	543	543	543	543	543	543	543
2	**Povidone**	30	35	40	38	37	30	35	40	38
3	**HPMCK4M**	40	80	120	140	160	160	160	160	160
4	**HPMC K15M**	40	40	40	40	40	160	140	120	80
5	**Talc**	7	8	5	7	7	7	8	5	7
6	**Magnesium stearate**	4	4	5	5	5	4	4	5	5

Table No.2- Comparative data of various formulations: Cefixime

S.NO	Ingredients(mg)	Trials								
		PF1	**PF2**	**PF3**	**PF4**	**PF5**	**PF6**	**PF7**	**PF8**	**PF9**
1	**Cefixime trihydrate**	227	227	227	227	227	227	227	227	227
2	**Povidone**	25	20	17	13	15	12	14	19	15
3	**Micro crystalline cellulose**	15	16	12	13	16	14	15	16	11
4	**Dicalcium phosphate**	-	20	20	22	17	21	20	22	19
5	**Tartrazine**	1	1	0.5	0.8	0.7	0.5	0.7	0.7	0.8
6	**Talc**	4	4	6	5	5	4	6	5	5
7	**Magnesium stearate**	6	6	4	5	5	5	5	4	4
8	**Cross carmellose sodium**	6	-	5	5	5	5	6	7	5
9	**Colloidal silicon dioxide**	1	1	1	1	1	1	1	1	1

Evaluation of Tablets:[6, 7, 8]

The prepared tablets can be evaluated for various official and non official specifications.

Thickness:

The thickness of the tablet is measured by vernier calipers scale. Thickness of the tablet related to the tablet hardness and can be used an initial control parameter.

Weight Variation:

Twenty tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the individual weight was compared with an average weight.

***in-vitro* Disintegration Time**:

A tablet was placed in each of the six tubes of the basket. Suspend the assembly in water maintained at a temperature of 37^0c ± 2^0c and operate the apparatus, simultaneously note the time taken to disintegrate completely by using stop watch.

***in-vitro* Drug Release Study:**

An in-vitro drug release study was carried out using tablet dissolution test apparatus USP type-2(paddle) at 100rpm.The dissolution medium consisted of 900ml phosphate buffer pH7.2, maintained at a temperature 37±0.5^{0}c. A sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced, and then measures the absorbance by HPLC technique.

Table No.3-Micromeritics properties of powder blend:

Formulation	Drugs	Bulkdensity (gm/cc)	Tapped Density (gm/ml)	Angle of repose(θ)	Compressibility index(%)	Hausner Ratio
F1	Dicloxacil	0.45	0.56	46.66	28.64	1.39
	Cefixime	0.44	0.55	50.12	27.00	1.44
F2	Dicloxacil	0.43	0.57	48.20	27.30	1.40
	Cefixime	0.49	0.51	46.56	28.33	1.38
F3	Dicloxacil	0.43	0.54	42.21	18.61	1.18
	Cefixime	0.49	0.50	38.65	18.90	1.19
F4	Dicloxacil	0.47	0.47	40.12	18.15	1.42
	Cefixime	0.46	0.45	42.13	18.95	1.44
F5	Dicloxacil	0.44	0.48	30.12	17.24	1.29
	Cefixime	0.44	0.47	28.13	15.69	1.26
F6	Dicloxacil	0.46	0.49	39.55	19.11	1.40
	Cefixime	0.43	0.50	37.10	20.24	1.36
F7	Dicloxacil	0.48	0.55	44.26	24.25	1.40
	Cefixime	0.48	0.51	47.39	21.29	1.43
F8	Dicloxacil	0.41	0.49	32.34	19.48	1.31
	Cefixime	0.45	0.50	37.91	18.90	1.43
F9	Dicloxacil	0.46	0.55	31.63	20.52	1.42
	Cefixime	0.47	0.53	31.28	24.33	1.34

Table No.4-Evaluation of tablets:

Formulation	Thickness (mm)	Weight variation (mg)	Hardness (Kp)	Friability (%)	In-Vitro Disintegration Time(mins)
F1	4.74	1081	12.6	0.645	6.48
F2	4.68	1065	12.2	0.782	6.74
F3	4.64	1079	11.4	0.571	5.86
F4	4.71	1048	11.6	0.623	5.60
F5	4.62	1085	13.1	0.553	7.03
F6	4.69	1092	12.8	0.351	6.90
F7	4.63	1072	14.3	0.480	7.48
F8	4.64	1086	13.9	0.580	6.88
F9	4.68	1090	13.2	0.439	6.93

Table No.5-Invitro dissolution profile of various formulations:

Time (Hours)	Innovator (Dicloxacillin)	Innovator (cefixime)	% Drug release of Dicloxacillin(F5)	% Drug release of Cefixime(F5)
1	15.55	97.57	15.87	96.62
4	49.98	99.10	48.38	97.18
8	64.77	99.97	62.90	99.10
12	94.10	101.04	92.71	101.24

Results and Discussions

In the present study Cefixime and Dicloxacillin Bi-layered tablet were prepared by wet granulation process by using ingredients shown in (table-1and table-2). A total number of nine formulations were prepared. The values of preformulation parameters evaluated were within prescribed limit and indicated good fine flow property (table-3). The data of evaluated tablets such as thickness, weight variation, hardness, friability, and In-vitro disintegration time, are shown in (table-4).The hardness was found to be in the range of 13kp to17kp, the normal acceptance criteria for hardness are not more than 25 Kp. The formulation F3, F4, F5, F9 has got hardness in the acceptable range and was consider acceptable upon comparing with the innovator product. All the formulations indicate good thickness except F1. The normal acceptable criterion for friability is not more than 1.0%. The formulation F3, F4 and F5 has got friability within the acceptable range. All the tablets passed weight variation test as the percentage weight variation was within the pharmacopoeial limits. The percentage drug release of Bi-layer tablets in F5 when compare with Cefixime innovator was found to be between 91.87 to 96.43%. The percentage drug release of Bi-layer tablets in F5 when compare with Dicloxacillin innovator was found to be between 15.87 to 92.51% and the results are shown in the table-5 along with figures 1, 2. While the in-vitro disintegration time was found in the range of 3.36 to7.41 min/sec. Formulation F4, F5, and F8 are nearly matched with the disintegration time of innovator product. Among the formulation tablets of batch F5 containing Cefixime 200mg and Dicloxacillin 500mg per tablet is similar and equal to the innovator product in respect of all tablets properties and dissolution rate and showed good hardness, low friability, and disintegration time of 4.35min/sec. The percentage drug release for formulation F5 shows the better drug release 92.51% at 12^{th} hour. It was concluded that Cefixime, Dicloxacillin Bi-layer tablets can be prepared successfully as it satisfies all the criteria as a Bi-layered tablet and would be alternative to the currently available conventional tablets.

Figure.1-Comparision of dissolution profile of Innovator Drug (Cefixime) and F5 (Cefixime) in pH 7.2 phosphate buffer:

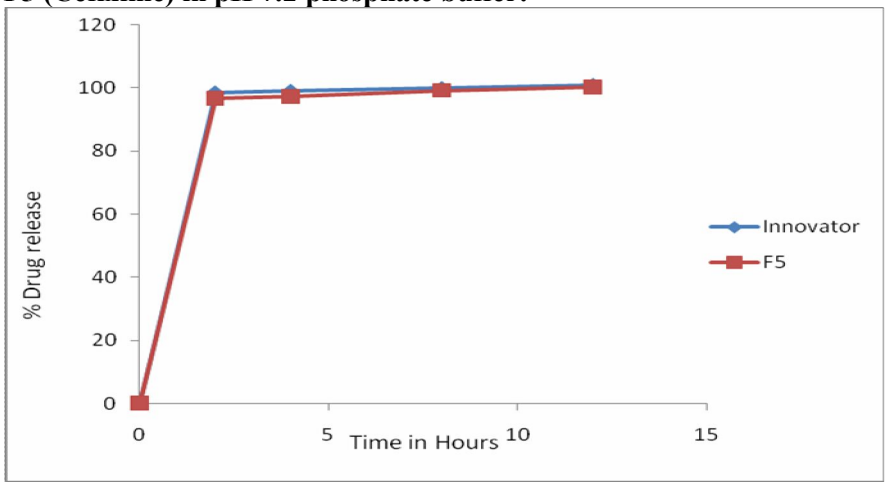
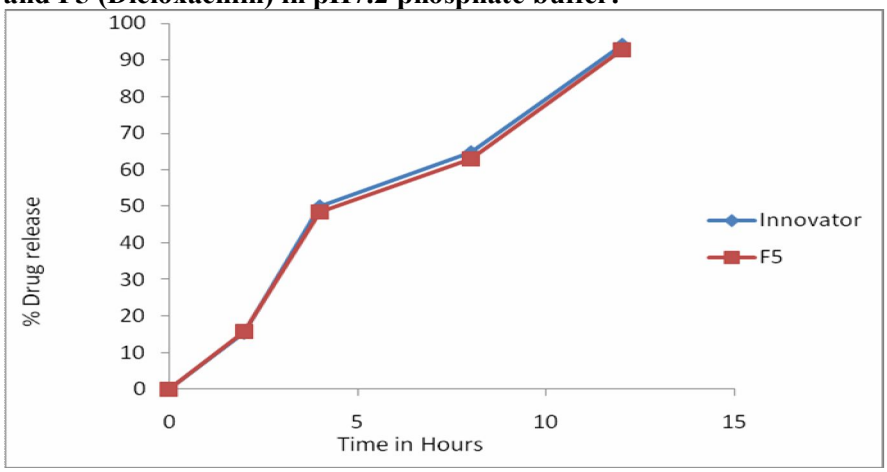


Figure.2-Comparison of dissolution profile of Innovator drug (Dicloxacillin) and F5 (Dicloxacillin) in pH7.2 phosphate buffer:



Acknowledgments

The authors are thankful to Aurobindo pharma, Hyderabad for providing gift sample of Cefixime and Dicloxacillin and other disintegrants.

References

1. Podczeck F., Drake K.R., Neton J.M., and Harian I., The strength of bi layered tablet.
European Journal of Pharmaceutical Sciences, 2008, 1-14.
2. Brahmankar D.M., Jaiswal B.S., Biopharmaceutics and pharmacokinetics A tretise, 2004, 335-347.
3. British pharmacopoeia 2009, Vol I and II, 1139-1143, 1897-1900.
4. Birringer N., Shoemaker s., Gilman C., Haynes M., and Plank R., Measurement and Optimization of layer adhesion in Bi-layer tablets, Pharmaceutical Development, Merck &Co.
5. Vishnu.M.Patel., HarshaV.patel, Bhupendra., Praji patil, Muchoadhesive Bilayer tablet of Propranolol Hydrochloride tablet, AAPS Pharm Scitech, 2007, 77, E1-E6.
6. Rahman Z., and Ali M., Design and Evaluation of Bi-layered tablets of Captopril, Acta Pharm, 2006, 56, 49-57.
7. Chinam N.P., Kumar A.B., Pandit H.K., Singh S.P., and Devi M.V., Design and Evaluation of Sustained Release Bilayer Tablets of Propranolol Hydrochloride. Acta Pharm. 2007, 57, 479-489.
8. Narendiran.C., Srinath M.S.,Ganesh babu., Optimisation of Bilayer floating tablet containing Metoprolol tartrate as a model drug for gastric retention, AAPS Pharm Scitech, 2006, 34, E1-E7.
9. Girish Sonar, Devandera K.Jain, Dhananjay M. More, Preparation and Invitro evaluation of Bilayer and floating-bioadhesive tablets of Rosiglitazone maleate, Asian Journal of Pharmaceutical Sciences, 2007, 2(4), 161-169.

10. AA.Shirwaikar., Sustained release Bilayer tablet of Diltiazem Hydrochloride using insoluble matrix system, International Journal of pharmaceutical Science, 2004, 66, 433-437.
11. Mohammed Rozasiah., Mohammed bar zagar-barali, Design and Evaluation of 1 and 3-layer matrices of Verapamil Hcl for sustaining its release, AAPS Pharma Scitech, 2006,1-3.
12. R.D.Kale., P.T.Tayade., Multiple unit floating drug delivery system of Piroxicam using Eudragit polymer, Indian Journal of Pharmaceutical Sciences, 2007, 69, 120-123.

*****