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Research Article

Formulation, Evaluation and Development of Bi-layer Tablet of Anti-Bacterial Drug *Ipomoea carnea* on Experimental Rats

Chandresh[1]*, Neeraj Sharma[1] and Shailesh Gupta [2]
1. Millenium College of Pharmacy, Bhopal, Madhya Pradesh, India
2. Millenium College of Pharmacy and Science , Bhopal, Madhya Pradesh, India

Abstract

The aim of present study is to formulate Cefotaxime sustained release (SR) and immediate release (IR) bilayer tablet by different concentration of Hydroxypropyl methylcellulose (HPMC) to control the release pattern. The sustained release layer of Cefotaxime was prepared by using different grades of HPMC like, HPMC K 4 & K 15, HPMC along with other excipients by direct compression technique. The immediate release layer of Cefotaxime was prepared by Cross carmellose sodium and Sodium starch glycolate by direct compression technique. The powders were evaluated for their flow properties and the finished tablets were evaluated for their physical parameters. The both immediate release and sustained release layers of Cefotaxime were characterized by FT-IR and in vitro dissolution studies.

The release rate of cefotaxime in immediate release layer was studied for1hin 0.1 N HCL media and that of cefotaxime in sustained release layer was studied for 12 h in pH 6.8 phosphate buffer media. From the nine batches S5 batch showed good release behavior 98.96± 0.12% of drug is released over 12 hours. Cefotaxime is a water soluble anti-bacterial drug. Due to the water solubility of this drug, its bioavailability is dissolution rate-limited. Total four trial batches of each drug have been manufactured to optimize and develop a robust and stable formulation, the stability studies of the products also comply with ICH guideline

Keywords: Bi-layer tablet, Sustain Release, Immediate Release, cefotaxime

Introduction : A tablet s a mixture of active substance and excipients usually in powder form pressed or compacted into a solid. The excipients includes binders, glidents (flow-aids), and lubricants to ensure efficient tableting, disintegrate to ensure that the tablet breaks up in the digestive tract; sweeteners or flavors to mask the taste of the bad tasting active ingredients and pigments.

*** Corresponding Author**
E.mail: Shailgpharma@gmail.com

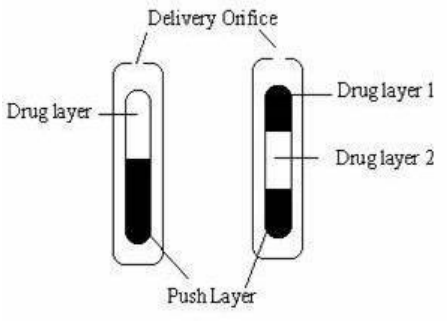
A coating may be applied to hide the taste of tablets components, to make the tablet smoother and easier to swallow and to make it more resistant to environment extending its real life. The compressed tablet s most popular dosage form in use today. About two third prescriptions are dispensed as sold dosage forms and half of these are compressed tablets. Bi-layer tablet is new era for successful development of controlled release formulation along with various features to provide successful drug delivery system. Bi- layer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles. The manufacture of bi-layer tablets, produced by sequential compaction of loose powder layers has become of increased interest within the pharmaceutical industry due to the increased release profiles of active ingredients that may be obtained. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as loading dose and second layer is maintenance dose. In case of bilayered tablets drug release can be rendered almost unidirectional if drug can be included in the upper non adhesive layer its delivery occurs into the whole oral cavity. The immediate release layer of bi-layer tablet has worked as the loading dose and the sustained release layer has maintained therapeutic plasma drug concentration for prolonged time. This article explains why development and production of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bilayer problems, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, reduced yield, etc

Methodology

OROS push pull technology

This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer (Fig.1). The drug

layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.



Bilayer and trilayer OROS Push pull technology

Evaluation of sustain release bi-layer

tablet Tablet Thickness and Size

Thickness and diameter of tablets were important for uniformity of tablet size.

Tablet Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness.

Friability

Friability is the measure of tablet strength. Electro lab EF-2 friabilator (USP) was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined.

Uniformity of weight

Twenty tablets were selected at random and the average weight was calculated. Weight variation was calculated and was compared with I. P. standards.

Dissolution Studies

Bi-layer tablets were subjected to in vitro drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. Drug release studies were carried out using USP dissolution test apparatus I at 100 rpm, 37 ± 0.5 ° C, and pH 1.2 buffer (900 ml) (ie 0.1 N HCl) for 2 hours, since the average gastric emptying time is about 2 hours . The dissolution medium was replaced with pH 6.8 phosphate buffer (900ml) and the experiment continued for another 10 hours. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer using multi component mode of analysis.

Preparation of Bi-layer tablet Selection of Method for Compression

The major challenge for tablet manufacture comes from the powder characteristics of material compressed. There are number of compression technology available in pharmaceutical industry. Tablets have been made by granulation, a process that imparts to be primary requisite to formulation for fluidity and compatibility on these bases granulation process can be divided as:

- **Dry granulation method.**
- **Direct compression.**
- **Wet granulation.**

Direct compression:

The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required.

FormulationDevelopment

Preparation of Instant Layer of Cefotaxime (Phase-1)

Fast dissolving tablets of Cefotaxime were prepared by direct compression method after incorporating different super disintegrants such as, crosscarmellose sodium (Ac- Di-Sol), crospovidone and sodium starch glycolate in different concentrations. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh # 60.

Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included Angle of repose, Bulk density, Tap density, Carr's index and Hausner'sratio.

The Blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine. Eight formulations of Cefotaxime granules were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablets weighing 150mg, were obtained.

Excipients like sodium bicarbonate, citric acid anhydrous, magnesium stearate were selected for the study. Sodium bicarbonate and citric acid were used as gas generating agent. Citric acid was also used as an antioxidant. Steps involved in the manufacture of tablets, first the drug, polymer and other excipients selected were passed through 40-mesh sieve. Required quantity of drug, polymer and excipients were weighed properly and transferred into polyethylene bag and the blend was mixed for at least 15 min. The blend obtained was then lubricated by adding 1% magnesium stearate and again mixed for another 5min

Result and discussion:

A dissolution study shows the release of Cefotaxime. The Bilayer control floating layer Cefotaxime shows release up to 12 Hours Approx 98.96±0.12 percent of Drug release

Bi-layer tablets provide one of the important design approaches where incompatible drugs, with different indication, and same drug with different release rate can be incorporated in a single unit. Each of the proposed bi-layer tablets is composed of an immediate-release layer and a sustained-release layer, anticipating rapid drug release that starts in the stomach to rapidly alleviate the symptoms and continues in the intestine to maintain protracted effect. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. The present study was to developed and evaluated bi-layer tablets of Cefotaxime. Cefotaxime is a third-generation cephalosporin antibiotic.

Conclusion:

Bi-layer tablets provide one of the important design approaches where incompatible drugs, with different indication, and same drug with different release rate can be incorporated in a single unit. Each of the proposed bi-layer tablets is composed of an immediate-release layer and a sustained-release layer, anticipating rapid drug release that starts in the stomach to rapidly alleviate the symptoms and continues in the intestine to maintain protracted effect. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. The present study was to developed and evaluated bi-layer tablets of Cefotaxime.

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Table No1 -Composition of Cefotaxime Fast Dissolving Tablets (Instant Layer)

Ingredients(mg)	**Formulation code**								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Cefotaxime	100	100	100	100	100	100	100	100	100
Sodium Starch glycolate	10	20	30	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	10	20	30	-	-	-
Crospovidone	-	-	-	-	-	-	10	20	30
Microcrystalline cellulose	29	19	9	29	19	9	29	19	9
Talc	5	5	5	5	5	5	5	5	5
Magnesiumstearate	6	6	6	6	6	6	6	6	6

Table No2 Results of Post-Compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
IF1	3.2	0.896	155	2.32	98.56
IF2	3.1	0.856	153	2.34	99.23
IF3	3.4	0.832	154	2.35	99.12
IF4	3.4	0.785	156	2.35	99.89
IF5	3.5	0.965	150	2.32	99.12
IF6	3.3	0.741	153	2.35	99.45
IF7	3.2	0.815	152	2.34	99.23

Table No3 Results of Post-Compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
IF1	3.2	0.896	155	2.32	98.56
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IF6	3.3	0.741	153	2.35	99.45
IF7	3.2	0.815	152	2.34	99.23

Table No4 -Preparation of Cefotoxamie gastro retentive layer

Excipients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefotaxime	150	150	150	150	150	150	150	150	150
HPMC K 4	50	80	110	-	-	-	25	40	55
HPMC K 15	-	-	-	50	80	110	25	40	55
PVP K30	10	10	10	10	10	10	10	10	10
Citric acid	5	5	5	5	5	5	5	5	5
NaHCO3	10	10	10	10	10	10	10	10	10
Mg(C18H35O2)2	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	65	35	5	65	35	5	65	35	5
Total Weight	300	300	300	300	300	300	300	300	300

Table No5- ***Results of Post Compression Properties of Cefotaxime FGR Tablets***

Formulation code	Thickness (mm)	Hardness (kg/cm2)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	3.85	5.2	305	0.658	98.85
F2	3.82	5.3	302	0.785	98.99
F3	3.78	5.4	310	0.658	98.65
F4	3.65	5.2	306	0.852	97.89
F5	3.79	5.4	308	0.658	98.45
F6	3.56	5.2	304	0.458	99.56
F7	3.65	5.3	306	0.658	98.89
F8	3.74	5.1	305	0.741	98.78
F9	3.58	5.2	306	0.954	99.12

Table No 6- Results of Evaluation of bilayer floatingtablets

Formulation	Hardness* test (kg/cm^2)	Friability* (%)	Weight Variation*	Thickness* (mm)
1.	5.8	0.568	Pass	4.2

Table No 7- Drug content

Formulation	Cefotaxime (% Label Claim)
In-house Bilayer floating tablet	99.25±0.45

Table No 8- Results of Dissolution rate studies of Floating layer

Time (Hour)	% Drug Release of Bilayer tablets
0.5	38.56±0.56
1	39.98±0.45
1.5	46.85±0.56
2	54.56±0.47
4	62.36±0.65
6	74.65±0.78
8	83.36±0.68
10	93.25±0.85
12	98.96±0.12