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STUDIES ON FORMULATION AND EVALUATION OF BILAYERED TABLETS OF CURCUMIN

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Keywords:

Bi-layer tablet, Curcumin, Superdisintegrants, Polymer, Direct compression, *In-vitro* dissolution study

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ABSTRACT: Bilayer tablet is a new era for the successful development of controlled release formulation along with various features to provide a way of the successful drug delivery system. Bilayer 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 bi-layered tablet is a very different aspect of anti-inflammatory and analgesic. The purpose of this study was to develop and evaluate bilayered tablets of curcumin for the effective treatment of inflammation. The Immediate-release layer was prepared by using superdisintegrants- SSG and binder used xantham gum and the sustained release layer was prepared by using hydrophilic polymer like HPMC K 100 and PVP. Before the preparation of the tablets, all the pre-formulation parameters were checked and the tablet of curcumin were prepared by direct compression method and was evaluated for physical characteristics like hardness, weight variation, drug content and friability. *In-vitro* release of drug was performed USP type I dissolution test apparatus using 0.1N HCl and phosphate buffer pH 7.4 as dissolution media and dissolution was continued for 12 h for the sustained release layer. It was found that all the formulations were within limit of the standard. The drug release of the tablet was in the range of 82.44% - 88.20% in 12 h. The rate of drug release follows the Higuchi model and First-order kinetics. It was concluded that the F4 formulation showed the optimum result as a bilayered tablet for the effective treatment of inflammation.

INTRODUCTION: Bilayer tablet is suitable for sequential release of two drugs in combination it is also capable of separating the two types of incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and the second player is maintenance dose [1].

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Bilayer tablet is a great example of avoiding chemical incompatibilities between the APIs and providing different drug release profiles (Immediate release with extended-release). In a bilayer tablet, amongst the two layers, the first layer acts for loading dose purpose and second will for maintenance purpose [2].

Curcumin is a bright yellow chemical produced by *Curcuma longa* plants. It is the principal curcuminoid of turmeric (*Curcuma longa*), a member of the ginger family, Zingiberaceae. It is solid as an herbal supplement, cosmetics ingredient, food flavoring, and food coloring. Curcumin mediates potent anti-inflammatory and

anti-carcinogenic actions via modulating various signaling molecules. It suppresses a number of key elements in cellular signal transduction pathways pertinent to growth, differentiation, and malignant transformation; it was demonstrated *in-vitro* that curcumin inhibits protein kinase, prostaglandin biosynthesis, and expression of the enzyme (COX)-2. Excretion is mainly by fecal excretion and also through biliary excretion in a small amount. Medicinal uses include they used as an anti-inflammatory, anti-oxidant, lower risk of brain diseases, preventing and treating Alzheimer's disease, rheumatoid arthritis, depression.

From literature, it is found that curcumin has anti-inflammatory properties and hence used in rheumatism but it has poor bioavailability due to its low aqueous solubility. To enhance its bioavailability, the present study is aimed to develop bilayered tablets of curcumin in which one layer serves immediate release as an initial dose and second layer as a maintenance dose for effective treatment of Inflammation.

In the present work, an attempt was made to prepare the bilayered tablet of curcumin by direct compression so as to increase its bioavailability and thereby reducing the dosing frequency.

MATERIALS AND METHODS:

Materials: Curcumin, dicalcium phosphate, hydroxypropyl methylcellulose, microcrystalline cellulose and xanthan gum were procured from Yarrow Chem Products Mumbai. All the other chemicals and reagents used in this study were of analytical grade.

Methods:

Drug-Excipient Interaction Study: A proper design and formulation of a dosage form require consideration of the physical, chemical and biological characteristics of both drug and excipients used in the fabrication of the product. Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious, attractive and safe product. So before producing the actual formulation, the compatibility of curcumin with excipients was tested using the Fourier Transform Infrared Spectroscopy (FT-IR) [3].

FT-IR Spectral Investigation: Samples of pure drug, IR layer composition, and SR layer composition were separately mixed with KBr to makes pallets for the IR spectra using Shimadzu FTIR 8400 spectrophotometer.

Formulation of Bilayer Tablet: In this study an attempt to prepared 6 formulations of curcumin, in all the 6 formulations the composition of immediate-release layer is the same and the sustained release layer varied.

Immediate Release Layer:

TABLE 1: COMPOSITION OF IMMEDIATE RELEASE LAYER

Ingredients	Quantity
Curcumin (mg)	20 mg
Xantham gum	10 mg
Sodium starch glycolate	12 mg
Dicalcium phosphate	24 mg
Microcrystalline cellulose	84 mg
Colorant	QS
Total	150 mg

Sustained Release Layer:

TABLE 2: COMPOSITION OF SUSTAINED RELEASE LAYER

Ingredients	F1	F2	F3	F4	F5	F6
Curcumin	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg
Poly vinyl pyrrolidone	0	0	10 mg	20 mg	10 mg	15 mg
Hydroxy propyl methyl cellulose	10 mg	20 mg	0	0	10 mg	5 mg
Xantham gum	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Micro crystalline cellulose	132 mg	132 mg	132 mg	132 mg	132 mg	132 mg
Total	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg

Preparation: The immediate-release layer was prepared by using super disintegrants-sodium starch glycolate and xantham gum as a binder and the sustained release layer was prepared by using hydrophilic polymer like HPMC K 100 and PVP. The various ratios of the ingredients used are shown in the formulation table, before the preparation of the tablets all the pre-formulation parameters were checked and the drug and excipients were mixed to get a premix for direct compression into tablets [4].

Evaluation of Prepared Bilayer Tablets:

Pre-compression Studies: The powder blends were evaluated suitably for their characteristic parameters such as the angle of repose, Hausner's ratio, bulk density, tapped density and Carr's index.

Post-compression Studies: As per pharmacopoeial procedures all batches of curcumin tablets were characterized for appearance, thickness, hardness, weight variation, friability.

Drug Content: 20 tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 320 mg of powder was weighed and dissolved in 100 ml of pH 7.4 phosphate buffer. From the stock solution, a 1ml sample was withdrawn and diluted to 10 ml with pH 7.4 phosphate buffer. The absorbance was measured at wavelength 432 nm using double beam UV-Visible spectrophotometer [5].

Disintegration Study: One tablet was introduced in the tube of disintegration apparatus and placed in 1litre beaker containing 0.1 N HCl at 37± 2 °C and the time of disintegration was recorded. The study was done at room temperature without the disc being added [6].

Dissolution Study: The dissolution test was carried out using USP Type I Dissolution apparatus (basket type). The stirring rate was 50 rpm. 900 ml of 0.1 N HCl was used as a dissolution medium which was maintained at 37 ± 0.5 ℃. 1 ml samples were withdrawn at 10 minutes interval for 1 h which was replaced with 1ml of fresh dissolution medium.

After 1 h the dissolution medium was replaced with 900ml of phosphate buffer pH 7.4 and was maintained at 37 ± 0.5 ℃. 1 ml of sample from each tube was withdrawn at the intervals of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 h and replaced with 1ml of fresh dissolution medium. The collected samples were analyzed and absorbance was measured at 432 nm by using UV spectrophotometer [7].

Stability Studies: The stability studies were carried out of the most satisfactory formulation as per ICH guidelines. The formulated bilayer tablets were kept at 25℃ ± 2 ℃ and at 40℃ ± 2 ℃ / 75 ± 5 % RH, for period of six months, and parameters evaluated hardness, friability, content uniformity, *in-vitro* disintegration time and *in-vitro* drug release [8].

RESULTS AND DISCUSSION:

Drug and Excipient Interaction Study: The FTIR studies were carried out as mentioned in the method. Major functional groups present in curcumin show characteristic peaks in IR spectrum.

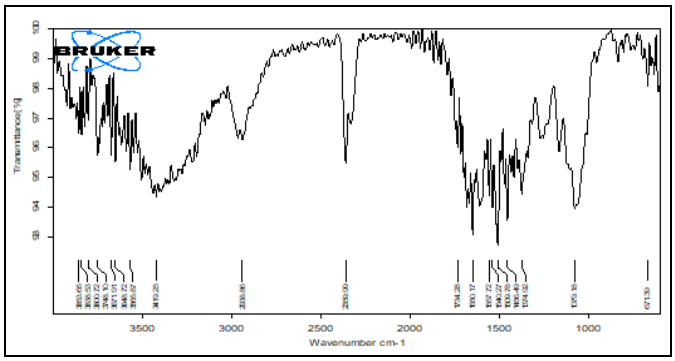

FIG. 1: FTIR SPECTRA OF CURCUMIN

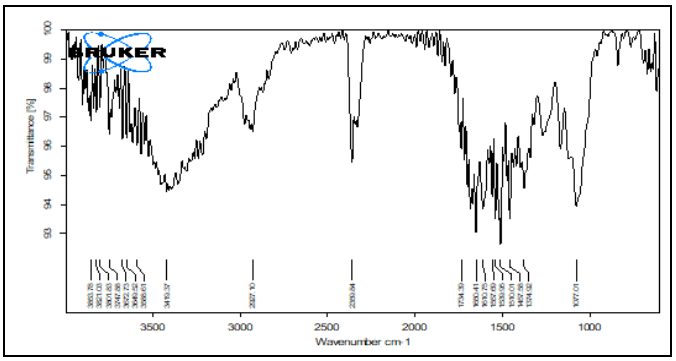

FIG. 2: FTIR SPECTRA OF CURCUMIN+ EXCIPIENTS

Fig. 1 showed an IR spectrum of curcumin having a characteristic absorption band. From the FTIR studies, the characteristic absorption bands for important functional groups of pure drug and physical mixture of drug and excipients can be identified. FTIR spectra showed that the characteristics bands of curcumin are not altered and can be successfully formulated without any change in their position, indicating no chemical interactions between the drug and excipients.

Pre-compression Studies:

Immediate Release Layer: Pre-formulation study of the IR batches are shown in **Table 3**, where bulk density is 0.51 gm/ml, tapped density is found to be 0.64 gm/ml, Carr's index is 10.31, Hausner's ratio was 1.10, angle of repose is 31.79°.

From these obtained results prepared blends were found to possess good flow properties and ready for compression into tablets.

TABLE 3: PRE COMPRESSION EVALUATIONS OF IR LAYER

Formulation	Bulk density*±SD	Tapped density* ±SD	Compressibility Index *±SD	Hausner's ratio*±SD	Angle of repose*±SD
IR Layer	0. 51±0. 001	0.64±0. 011	10.31±0.18	1. 10±0.051	31.79±0.414

*Average of six determinations, SD-Standard deviation

Sustained Release Layer: Pre-formulation study of the SR batches are shown in **Table 4**, where bulk density in the range of 0.47-0.51 gm/ml, tapped density shown in the range of 0.62-0.67 gm/ml, Carr's index was 12.41-13.78, Hausner's ratio was 1.09-1.12, angle of repose is 36.97-38.39º. The results of the prepared blends showed that they possess good flow properties and ready for compression into tablets.

TABLE 4: PRE-COMPRESSION EVALUATIONS OF SR LAYER

S. no.	Formulation	Bulk density*±SD	Tapped density*±SD	Compressibility Index *±SD	Hausner's ratio*±SD	Angle of repose*±SD
1	F1	0.49±0.003	0.66±0. 011	12.41±0.20	1.10±0.01	38.39±0.456
2	F2	0.47±0.005	0. 62±0.01	12.82±0.367	1. 09±0. 02	37.53±0.671
3	F3	0.50±0.0051	0.62±0.017	12.92±0.290	1.12±0.030	38.70±0.579
4	F4	0.51±0.0050	0. 67±0.015	13.20±0.235	1.11±0.072	36.97±0.715
5	F5	0.50±0.01	0.65±0.01	13.13±0.215	1. 12±0.025	37.12±0.527
6	F6	0.49±0.015	0. 63±0.025	12.78±0.325	1.10±0. 020	37.03±0.717

*Average of six determinations, SD-Standard deviation

Post-compression Studies:

General Appearance: The formulated curcumin bilayered tablets were round in shape with immediate-release layer orange in color and sustained release layer yellow in color as seen in the figure and with a distinctive odor.

The tablets were subjected to evaluation tests according to IP standards. The hardness of tablets from each batch of the formulation was found to be in the range of 5.4 to 6.5 kg/cm^2. The thickness of all bilayered tablets was tested. It was observed that the thickness of all tablets ranged between 2.3-2.6 mm. The weight variation test was performed. The weight variations of the sample were found to be within the range of 350 ± 0.577 to 360 ± 1.527 mg. The friability was less than 1% for all the batches of tablets. The evaluation values are shown in **Table 5**.

Content Uniformity: In all the prepared batches on which the content uniformity tests were carried out. The drug content was found in the range of 93.6-98.50%.

FIG. 3: CURCUMIN BILAYERED TABLETS

TABLE 5: POST-COMPRESSION STUDIES OF F1-F6 BATCHES

Batches	Thickness (mm) ±SD	Hardness (kg/cm^2) ±SD	Weight variation (mg) ±SD)	Friability (%) ± SD
F1	2.5 ± 0.0471	3.5 ± 0.257	350 ± 1.527	0.268 ± 0.001
F2	2.6 ± 0.05	3.8 ± 0.09	350 ± 0.577	0.301 ± 0.006
F3	2.3 ± 0.076	3.4 ± 0.07	356 ± 1.01	0.286 ± 0.005
F4	2.6 ± 0.09	3.7 ± 0.05	350 ± 2.08	0.281 ± 0.001
F5	2.5 ± 0.052	3.8 ± 0.3	360 ± 1.527	0.314 ± 0.005
F6	2.5 ± 0.050	4.2 ± 0.4	350 ± 3.511	0.297 ± 0.001

Values are mean ± SD, n=3

Disintegration Time: The disintegration time of formulations F1 to F6 of the Immediate-release layer was determined using the disintegration test apparatus. The time taken for the disintegration of the prepared formulation is shown below **Table 6**. It was observed that the disintegration time of all tablets ranged between 32-38 sec.

TABLE 6: DISINTEGRATION OF F1 - F6 OF PREPARED IR FORMULATION

Formulation	Disintegration time (in sec)
F1	37±2.16
F2	35±1.632
F3	33±0.816
F4	32±2.05
F5	35±1.699
F6	38±1.247

In-vitro Dissolution Studies:

Immediate Release Layer: The release of curcumin from the immediate-release layer was analyzed by plotting the cumulative percentage of drug release *vs.* time.

The immediate-release layer produces an effective initial burst and provides good release within 60 min. The F4 layer produces a 93.60% release.

Sustained Release Layer: Formulations F1, F2 were prepared using HPMC K100. F3 and F4 were prepared using PVP, F5 and F6 were prepared by using HPMC K100 and PVP. In each formulation, the quantity of HPMC K100 and PVP was varied to achieve the desired drug release profile. In formulation, F1 and F2 HPMC K 100 was used which produced 82.44 and 87.84% respectively in 10 h. In formulation, F3 and F4 PVP produced 84.24 and 88.98% respectively. But the use of HPMC K 100 and PVP produced 83.52 and 86.76% respectively in 10 h for F5 and F6. Hence the formulation F4 containing PVP showed maximum drug release (88.98%). Hence, it shows that an increase in the concentration of PVP as in the case of formulation F4 achieved the better release of the drug.

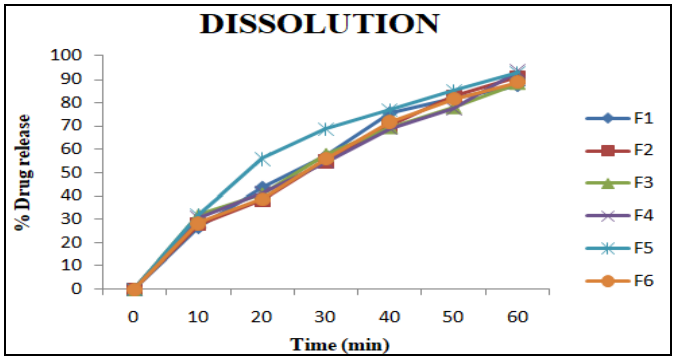

FIG. 4: DISSOLUTION PROFILE OF IMMEDIATE RELEASE LAYER OF THE PREPARED FORMULATION

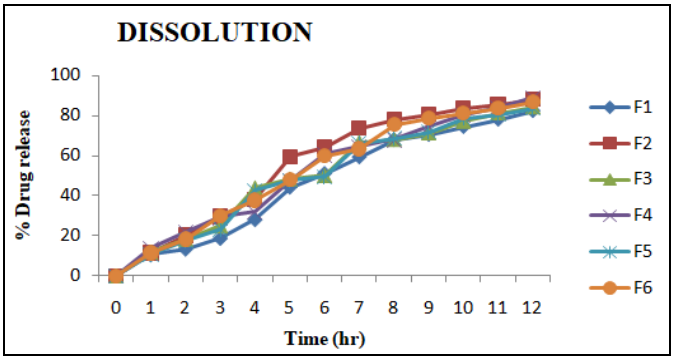

FIG. 5: DISSOLUTION PROFILE OF SUSTAINED RELEASE LAYER OF THE PREPARED FORMULATIONS

Kinetic Release Profile: Kinetic studies of the formulation F4 was carried out. Various models like zero order, first order, Higuchi model, and Korsmeyer Peppas model were used.

From the analysis of kinetic data, formulation F4 was found to follow the First order release with the Higuchi model release.

TABLE 7: R^2 VALUE OF KINETIC MODELS

Formulation	Kinetic models			
F4	Zero order	First order	Higuchi Model	Korsmeyer-Peppassss Plot
R^2	0.970	0.980	0.978	0.857

Stability Studies: F4 was selected as the best formulation and was chosen for stability studies. Stability study was conducted at 25°C ± 2°C/ 60% RH ± 5% RH and 40 ºC ± 2 °C / 75 ± 5 % RH for 6 months and parameters evaluated for hardness, friability, content uniformity, *in-vitro* disintegration time and *in-vitro* drug release for the best formulation F4. From the evaluations, it was found that there were no significant changes in hardness, friability, disintegration time, *in-vitro* drug release study.

TABLE 8: STABILITY STUDY AT 40°C ± 2°C / 75% RH ± 5% RH

Parameters studied	Initial	3rd month	After 6th month
Physical appearance	Orange and yellow colour	Orange and yellow colour	Orange and yellow colour
Hardness	5.7 ± 0.05	5.8 ± 0.05	5.8 ± 0.05
Friability	0.281 ± 0.001	0.281 ± 0.001	0.281 ± 0.001
In-vitro disintegration time	32 ± 2.05	32 ± 2.05	32 ± 2.05
Content uniformity	98.5 ± 0.50	98.5 ± 0.50	98..3 ± 0.50
In vitro drug release	88.98	88.20	87.82

CONCLUSION: The present work involves the formulation and evaluation of bilayered tablets of curcumin using HPMC K 100 and PVP as a retardant polymer. The drug-excipients compatibility studies confirmed that the drug is compatible with selected polymer HPMC K 100 and PVP. The pre-compression parameters and post-compression parameters were obtained from both the layers and were within the acceptable limits. The tablets were prepared by direct compression method. The post-compression parameters were within the prescribed limits.

Optimized formulation design of curcumin bilayered tablets was successfully developed and manufactured and all parameters were closely monitored and evaluated. The amount of PVP and HPMC K100 were selected as the main factor for optimization. While studying the IR spectrum there was no significant change in the peak of the curcumin, therefore it was concluded that there was no interaction between drug and other excipients. The post-compression studies were within the prescribed limits of pharmacopeial specifications. The tablets showed an immediate release to provide the loading dose of drug followed by sustained release up to 12 h. The *in-vitro* drug release from the tablets show significantly improved drug dissolution. Among the 6 formulations prepared, the formulation F4 has shown 88.98% release and it can be considered as the best formulation.

Kinetic release studies of the best formulation were better explained by the First order and Higuchi model and it indicated that the release of drugs from the formulation is through diffusion mechanism. Stability studies indicate that formulation remained stable and no significant change was observed before and after stability studies. Hence, this optimized bilayer tablet dosage form could be a potential formulation for the delivery of drugs from a single dosage form which could reduce the dosing frequency, improve patient compliance and give better disease management. There is no hindrance for large scale production of bilayer tablets from industrial standpoint.

Besides this, preparation is cost-effective when compared with other controlled release dosage forms. Hence, this tablet will definitely throw a new focus of attention for researchers who are interested to design modified sustained release dosage form in a cost-effective manner.

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