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Formulation and Evaluation of Indomethacin Bilayer Sustained Release Tablets

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Abstract: The objective of the present investigation was to develop a bilayer-floating tablet (BFT) for Indomethacin using direct compression technology. Bilayer tablets were punched using optimized solid dispersion, HPMC K4M, Avicel PH-112, ac-di-sol, magnesium stearate and aerosil in fast release layer and optimized floating layer as sustained release layer. Tablets were evaluated for physico-Chemical properties such as Hardness, Friability, Thickness, weight Variation and drug content uniformity. FT-IR studies revealed that there was no interaction between the drug and polymers used in the study. In Vitro dissolution studies were carried out in a USP type II Paddle type apparatus. The optimized formulation (A2) showed no significant changes on stability studies when storing at 4º c, 40º c, /75%RH, 60º c/80% RH for 3 months. The release data obtained from the dissolution study of the bilayer tablets were analysed with respect to first order model, Higuchi model, Korsmeyer-Peppas model, and zero order models. In this study optimized formulation (A2) release the drug up to 24hrs and fulfilled many requirements such as easy to fabricate, cost effective and high patient compliance.

Key words: Ac-di-sol, Avicel PH-112, bilayer tablets, indomethacin.

Introduction

Modified release dosage form is a general term used to describe the dosage forms having drug release features based on time, course and/or location and which are designed to accomplish therapeutic or convenience objectives not offered by conventional or immediate release forms. There are several terms which are used interchangeably with respect to modified release dosage forms, viz., controlled release, sustained release, prolonged release, extended release and other such dosage forms. Controlled release system differs from other systems which simply prolong the drug release and hence the plasma drug levels for an extended period of time. Controlled release systems are those which can provide some control, whether this is of a temporal or spatial nature, or both, of the drug release in the body. An ideal controlled release system aims at delivering the drug at a predetermined rate, locally or systemically, for a specified period of time.[1-2]

The design of controlled release dosage forms holds many advantages over conventional dosage forms like Reduction in frequency of drug administration, improved patient compliance, Reduction in drug level fluctuation in blood, reduction in total drug usage when compared with conventional therapy.[3-4]

Bilayer tableting technology has been specially developed to provide two different release rates or biphasic release of a drug from a single dosage form. For these types of drugs, extended release formulations generally lead to a delayed appearance of effective plasma levels and they cannot provide a prompt disposition of the dose immediately after administration.[5] To fulfil the specific therapeutic needs of the different diseases, new drug delivery devices are required for a more accurate time-programmed administration of the active ingredients. The optimization of pharmaceutical formulations with regard to one or more attributes has always been a subject of importance and attention for pharmaceutical scientists in formulation research.[6]

Indomethacin is a methylated indole derivative (2-[1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl] acetic acid) (Fig.1) and a member of the arylalkanoic acid and is a non-steroidal anti-inflammatory drug. Physico-Chemical properties and Biological properties of indomethacin help us to making formulation of sustained release easily. The plasma half-life of Indomethacin is 2.6-4.5 hours. It is potent antipyretic, analgesic, and anti-inflammatory drug. Indomethacin is nonselective COX inhibitor. It is a highly potent inhibitor of prostaglandin synthesis and suppresses neutrophil activity.[7-10]

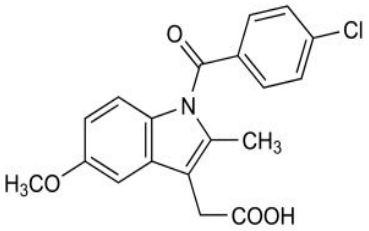


Fig. 1: Chemical Structure of Indomethacin

Among the various hydrophilic polymers, hydroxyl propyl methylcellulose (HPMC) was selected for the development of sustained release floating tablet of indomethacin considering that they are most widely used, non-ionic and versatile polymers. HPMC works well with soluble and insoluble drugs and at high and low dosage levels. They are tolerant of many variables in other ingredients and production methods. Lactose as diluent, sodium bicarbonate as gas generating agent, polyvinylpyrrolidone (PVP) solution as binder, magnesium stearate as lubricant and aerosil as glidant were selected.

Materials

Indomethacin was obtained as a gift sample from Nobel Pharmaceutical Company (Turkey), India. HPMC K100LV, HPMC K4M AND HPMC K15 M were obtained from Ranbaxy Laboratories Ltd., India. All the polymers received were of pharmaceutical grade. Other materials and solvents used were of analytical grade or better. All the studies were carried in HPLC grade water.

Preformulation studies

The melting point of indomethacin drug sample was determined the parameters like melting point, identification of pure drug indomethacin by UV spectra, IR spectra (Fig.2) , solubility, drug excipients compatibility studies, angle of repose, bulk density, tapped density , Hausner ratio, Carr's index and loss on drying were evaluated.[11,12]

Compatibility studies

Indomethacin granules with various excipients in glass vials were taken and kept at various
accelerated condition (30˚c/ 65% RH, 40˚ c / 75%RH and60˚c / 80%RH) in stability chamber for three months in open and closed condition. The sample were withdrawn on 1st, 2nd, 3rd 4th, 5th 6th, 7th 14th 21st and 30th day and physical characteristics like colour change if any was recorded . Finally the mixtures with no colour change were selected for formulations.

Preparation and Characterization of Bilayer tablets

All the ingredients except magnesium stearate and aerosil were sifted through a 60-mesh sieve. The ingredients were mixed by geometric dilution technique. After blending, granulation was done using sufficient quantity of alcoholic polyvinyl pyrrolidone (PVP K-30) solution. The wet mass was first passed through a 12-mesh sieve and then granules were dried in an oven at 45^{o}C for 90 min. The granules were passed through a 25-mesh sieve. Finally the granules were lubricated with magnesium stearate and aerosil for 3 min. The bilayer tablets of Indomethacin were prepared by direct compression method. The drug and polymers for both fast release and sustaining layer, shown in table.1 and table.2 were passed through a 180 mm seize before their use in the formulation.[13]

Characterization of granules

Prior to compression, granules were evaluated for their characteristic parameter such as tapped density, Carr's Index and angle of repose. Carr's compressibility index was calculated from the bulk and tapped density using a digital tap density apparatus (Electrolab India).

Table 1: Composition of Fast Release layer in Bilayer tablets

S. No.	Ingredient	Quantity (mg)
1	Solid dispersion (1:6)	140
2	Avicel PH-112	55
3	Magnesium stearate	3
4	Aerosil	2

Table 2: Composition of Sustained Release Floating layer in Bilayer tablet

S. No.	Ingredient	Quantity (mg)
1	Indomethacin	55.00
2	HPMC K4M	30.00
3	Ac-di-sol	19.42
4	Sodium bicarbonate	22.53
5	Lactose anhydrous	69.00
6	PVP- K30	q.s.
7	Magnesium Stearate	2.00
8	Aerosil	2.00
9	Colour (red oxide of iron)	q.s.

Compression of Bilayer tablet

The quantity of granules for the sustained release layer was compressed lightly using a single punch tableting machine (Cadmach machinery Co. Pvt. Ltd) equipped with 9 mm round flat and plain punches. Over this compressed layer the required quantity of the fast release layer was placed and compressed to obtain hardness in the range of 5 – 6 kg/cm^2 to form a bilayer matrix.

Physical tests for Bilayer tablets

Standard physical test for the bilayer matrix tablets were performed and average values were calculated. 20 tablets were individually weighed and then their average weight was calculated. The average weight was compared with the individual tablet weights and the weight variation was calculated. The hardness of the prepared tablets was determined by using Monsanto tablet hardness tester. (Royal scientific Pvt. Ltd. Chennai.) Twenty tablets of the floating layer were weighed, introduced into the plastic chamber of a friability apparatus (Electrolab, Mumbai), the apparatus was operated for 4 minutes at 25 rpm. Floating lag was determined using a glass beaker filled with 250 ml 0.1 N HCl.[14]

Drug Content Uniformity

Ten tablets were finely powdered and an amount equivalent to 100 mg weighed & transferred to 100 ml volumetric flask and 70 ml of methanol was added. The flask was shaked for 10 min. Finally the volume was made up to mark with methanol and analyzed in U.V Spectrophotometer. (Elico Ind, Ltd. India) at 275nm.

Dissoluton test

Release of the prepared tablets was determined up to 12 hr. using U.S.P. XXIV (type II) dissolution rate test apparatus (Model TDT 6P Electrolab Mumbai, India). Nine hundred ml of 0.1 N HCl containing 0.5% SLS was used as dissolution medium. The rotation of paddle was fixed at 75 rpm and the temperature of 37 $\pm$ 0.5ºC was maintained throughout the experiment. Samples of 10 ml were withdrawn at known time intervals and were replaced with same volume of fresh dissolution media after each withdrawal. The samples were analyzed spectrophotometerically for drug contents on double beam UV/Visible spectrophotometer (Shimadzu 1700) at 320 nm).[15]

Assay

20 tablets were weighed and crushed using mortar and pestle. The powder weight equivalent to 55 mg was dissolved in 10 ml methanol in a 100 ml volumetric flask and allowed to stand for 10 minutes. Then, 7.2 pH phosphate buffer was added and volume was made up to 100 ml which was then filtered through whatman filter paper # 41. Five ml of this resulting solution was further diluted to 100 ml with 7.2 pH phosphate buffer. The absorbance was taken in UV-visible spectrophotometer at 320 nm using 7.2 pH phosphate buffer as blank.

Stability testing of Indomethacin Bilayer tablet formulation

The formulated indomethacin bilayer tablets were kept at different storage conditions. The control samples were kept at 2-8^{0}C and test samples were kept at room temperature and at 40^{o}C/75% RH. The drug content of the tablets was determined initially and then at the interval of 15 days and one month.[16]

Mechanism of Drug Release

Korsemeyer desired a simple relationship which described drug release from a polymeric system equation to find out the mechanism of drug release, the drug release data was fitted in Korsemeyer –Peppas model.[17]

Table 3: Evaluation of the Prepared Bilayer tablets

S.No.	Parameter	Result
1	Bulk Density (gm/cm^3)	0.533-0.57
2	Tapped Density (gm/cm^3)	0.666-.687
3	Compressibility Index	>15.0
4	Hausner Ratio	1.247
5	Angle of repose	32º

Table 4: Evaluation of Parameters of Prepared Bilayer tablets

S.No	Parameter	Results
1	Floating lag time (seconds)	278
2	Total floating time (hrs.)	8.50
3	Weight variation (mean$\pm$ S.D) (mg)	403.3 $\pm$ 2.7
4	Hardness (Kg/cm^2)	4.5-5.5
5	Friability (%)	0.26

Fig.2.FTIR Spectrum of Indomethacin drug sample

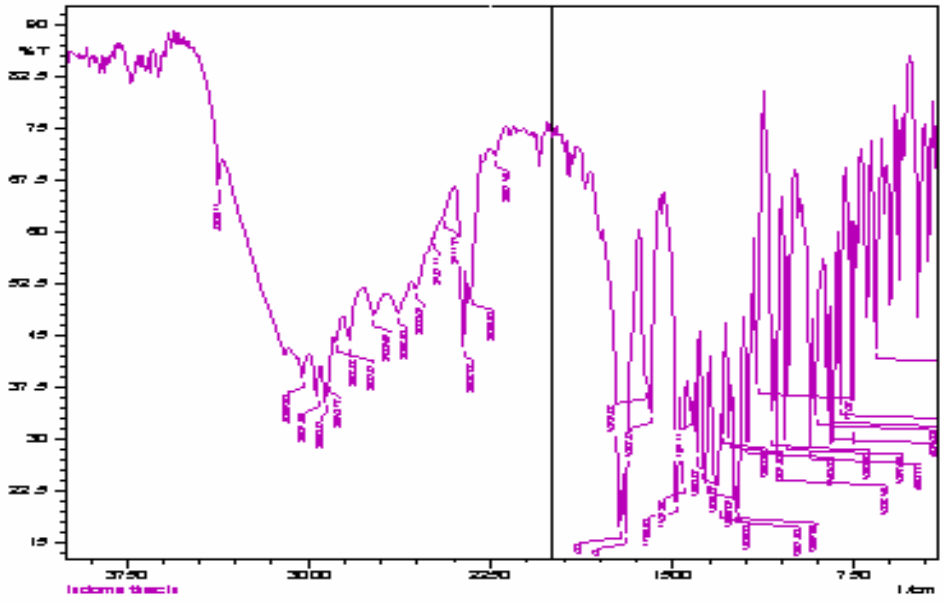


Fig. 3: Release Profile of drug from Bilayer tablet

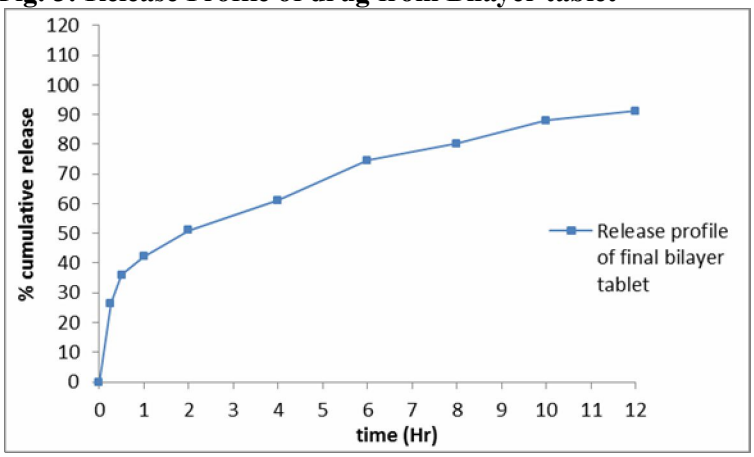


Fig.4: HIGUCHI plot of the Indomethacin Bilayer tablet

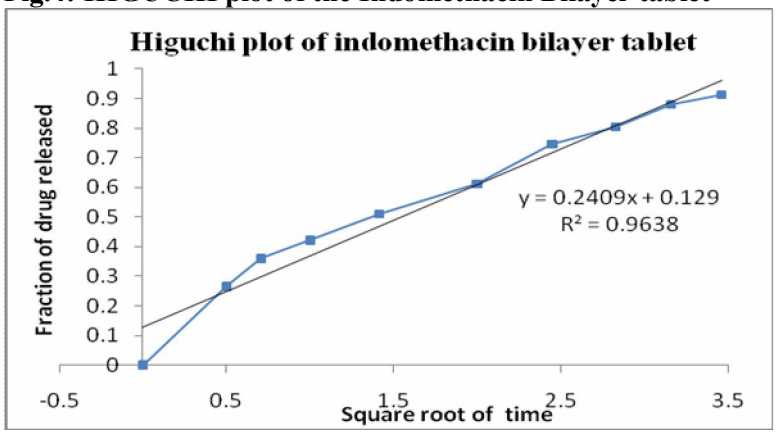
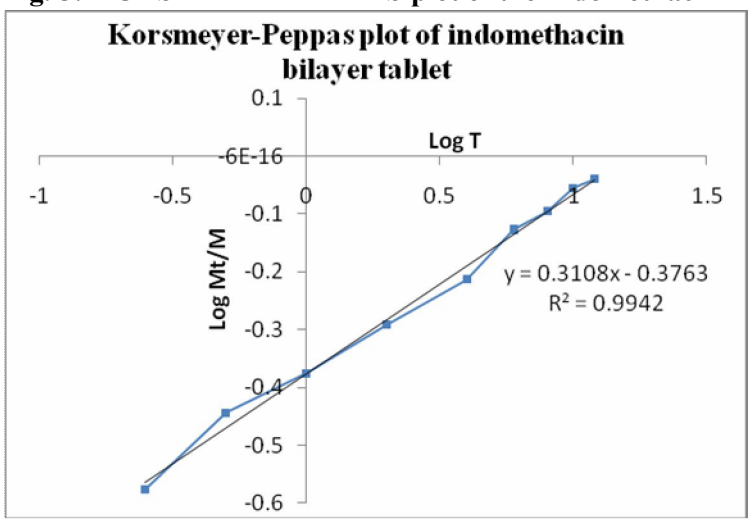


Fig. 5: KORSMEYER-PEPPAS plot of the Indomethacin Bilayer tablet



Result & Discussion

The prepared bilayer tablets were evaluated for various physical properties. The bulk density for the granules of various formulations ranged between 0.533 -.0.573 gmL-1 as determined by the tap method. This value of bulk density indicates of good packing character. The compressibility Index (CI) for formulation was found to be below 15% indicating desirable flow properties (Table.3). The flow properties of granules were further analysed by determining the angle of repose for all granules. It ranged between 32^{O}C-33^{O}C. Average weight, hardness and thickness of tablets were 403.3 $\pm$ 2.7mg + 5 hardness was 4.5-5.5 kg/cm^2 + 1.2 and thickness was 3.7 mm. + 0.1 The percentage friability of all formulation was 0.26 + 0.01% values of percentage friability (Table.4) indicate good handling properties of the prepared bilayer tablets. The drug content uniformity in bilayer matrix tablets was 98.24% + 0.31. FT- IR spectrum of Indomethacin bilayer sustained release tablets revealed there is no major interaction between drug and polymers used in the study. The release of Indomethacin from fast releasing layer was analysed by plotting the cumulative percentage drug release vs. time. It shows an initial burst effect. From all the formulation over 30% of indomethacin was released within 2 hrs. of dissolution study was showed in (Fig.3)

In this formulation, the calculated regression coefficient for Higuchi, Peppas models were 0.991, 0.967 respectively. Therefore the release seems to fit the Higuchi model was showed in (Fig. 4). Higuchi's Plot, Peppas's Plot (Fig.5) states that release followed the diffusion controlled mechanism.Bilayer tablets passed the weight variation and friability test. Hardness was also within desired limits. The tablets showed good total floating time and in-vitro release profile. However, bilayer tablet showed considerable increase in the floating lag time than the single layer floating tablet. This could be due to increase in the tablet weight (from 200 mg to 400 mg).

Slow disintegration of fast release layer was also observed due to the waxy nature of PEG-6000. It was decided to incorporate ac-di-sol in fast release layer which would quickly disintegrate it and decrease the floating lag time.The final indomethacin bilayer tablet showed the desired in-vitro release profile (Table.5). Two different drug release phases were observed. The tablet provided around 25 mg of dose during first 30 minutes and sustained the release of remaining dose for the next 12 hours. The indomethacin bilayer tablet formulation was found to be stable under the conditions of room temperature and 40ºC for the period of three months at least (Table.6).

Table 5: Dissolution data of drug from Bilayer tablet

S.No	Time (hr)	% Cumulative drug release
1	0	0
2	0.25	26.54
3	0.50	35.98
4	1	42.13
5	2	51.07
6	4	61.21
7	6	74.67
8	8	80.27
9	10	88.04
10	12	91.23

Table 6: Stability data of Indomethacine Bilayer tablet formulation

Storage conditions	Percentage drug content at various time intervals		
	Day 0	Day 15	Day 30
Control (2-8^{o}C)	98.24	98.00	97.88
Room temp. (25^{o}C)	98.24	97.78	97.54
40^{o}C	98.24	97.93	97.12

Conclusion

The present research was carried out to develop a bilayer tablet of indomethacin using PEG-6000 as disintegrant and ac-di-sol for fast release layer. Bilayer tablets showed an initial burst effect to provide the loading dose of drug, followed by sustained release for 24 hrs. This modified release bilayer tablets also reduced dosing frequency, increase the bioavailability and provide better patient compliance. The present work was to apply the mixed solvency concept in increasing the solubility of poorly water-soluble drug. Solid dispersion can be prepared by mixed solvency concept, which can increase the dissolution rate of drug. Availability of the drug in solubilized state will ensure its quick absorbtion.

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