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Design and evaluation of mucoadhesive controlled release oral bilayer tablets of indomethacin using solid dispersion

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ABSTRACT

In the present investigation mucoadhesive oral controlled release tablets of indomethacin were formulated for prolong anti inflammatory and antipyretics with analgesic action. Matrix tablets of indomethacin were formulated using two mucoadhesive polymers namely carbopol 934 LR and hydroxyl propyl cellulose. Solubility of Indomethacin was increased by solid dispersion using PEG 6000. Two layered tablets formulation, designed with an immediately releasing layer containing loading dose (25 mg Indomethacin) using a super disintegrate Ac-Di-Sol and a sustain releasing layer (75 mg Indomethacin) using Carbopol 934 LR or hydroxyl propyl cellulose. Carbopol 934 LR mucoadhesive polymers gave better controlled drug release compare to hydroxyl propyl cellulose and mixture of Carbopol 934 LR and Hydroxyl propyl cellulose as 1:1 in mucoadhesive controlled release oral bilayer tablets of indomethacin.

Keywords: Carbopol 934 LR, Indomethacin, Mucoadhesive, Solid Dispersion.

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INTRODUCTION

Indomethacin (IDM) is a very effective anti-inflammatory and antipyretic drug with analgesic property. But, when taken orally against chronic inflammatory and pain conditions, adverse events often occur, such as general serious gastrointestinal reaction (even stomach perforation), central nervous system symptoms, liver function damage, inhibition of hematopoeitic system and allergic reaction [1]. Meanwhile, its inconvenience in use is also a problem, such as pretty high frequency of administration (25 mg) and long period of treatment [2]. Hundreds of papers have been published in terms of its new carriers and new dosage forms to reduce its side effects and to enhance its therapeutic efficiency, such as nano-encapsulated microparticles [3], chitosan microspheres [4], spray-dried powders of polymeric nanocapsules [5] and suppository [6]. Entric-coated tablets, cream, patches, capsules [7], suppository and liniment of IDM are all collected in the Pharmacopoeia of China [8].

Mucoadhesive controlled release oral tablets of indomethacin have been stated to reduce the incidence and severity of both gastrointestinal and CNS side effects compared to conventional oral tablets and capsules formulations of this drug [9]. In published studies concerning the applications of mucoadhesive tablets, the tablets have been most often compressed without adjuvants. When Carbopol 934 LR or HPC was used, a non disintegrating and insoluble matrix tablets was formed during the compression. The greatly reduced porosity and surface area prolonged the release of the drug from tablets [10].

In the present investigation mucoadhesive oral controlled release tablets of indomethacin were formulated employing carbopol 934 LR and hydroxyl propyl cellulose. These materials are reported to have good mucoadhesive properties. Mucoadhesive polymers prolong the residence time of the dosage form in the gastrointestinal tract and hence are more suitable as matrix materials for oral controlled release. The tablets were evaluated for controlled release kinetics, mechanism and in vitro mucoadhesive property. The in vitro drug release rates of the optimized tablets were fitted in pharmacokinetic model [11].

MATERIALS AND METHODS

MATERIALS

Indomethacin, Carbopol 934 LR [12], Hydroxyl Propyl Cellulose, Ac Di Sol, PEG 6000, Lactose, Talc, Magnesium Stearate all the ingredients are laboratory grade and procured from yarrow chemical Products, Mumbai.

METHODOLOGY

Preparation of indomethacin solid dispersion

PEG 6000, 10 gm, was melted at 60º C. 10 gm of indomethacin were added with stirring to form a homogenous mass. The mixture was cooled to room temperature for 2 days. The

resulting mass was powdered, and screened through a No. 40 mesh sieve. The given dispersion was used for preparing tablets [13, 14].

Preparation of spray dried lactose

Lactose dissolved in pure water on water bath at 45-50 ºC until the solution was supersaturated. After that immediately cool the solution in ice, filter it and dried it. The given lactose was called as spray dried lactose which is used in direct compression of mucoadhesive tablets.

Preparation of indomethacin mucoadhesive tablets

Mucoadhesive matrix tablets each containing 75 mg of indomethacin were prepared by direct compression employing carbopol 934 LR and Hydroxyl Propyl Cellulose as mucoadhesive polymers as per the formulae given in table 1. All ingredients were mixed including solid dispersible indomethacin for 10 mins. They were compressed into 200 mg tablets to a crushing strength of 4.5-5.5 kg/cm^2 on Rimek Minipress rotary tablet compression machine at room temperature using 9 mm flat surface punches. All the prepared tablets were evaluated for crushing strength, friability, content uniformity, weight variation and disintegration time. Disintegration was determined using water, 0.1 N HCl as the test fluids.

Table No.1 Composition of different SR layer tablets

BATCH	B1	B2	B3	B4	B5	B6	B7	B8	B9
Solid dispersible indomethacin	100	100	100	100	100	100	100	100	100
Carbopol 934 LR	25	37.5	50	50	75	100	-	-	-
Hydroxy Propyl Cellulose	25	37.5	50	-	-	-	50	75	100
Talc	1%	1%	1%	1%	1%	1%	1%	1%	1%
Mg. stearate	2%	2%	2%	2%	2%	2%	2%	2%	2%
Spray Dried Lactose	q.s. to 200	q.s. to 200	q.s. to 200	q.s. to 200	q.s. to 200	q.s. to 200	q.s. to 200	q.s. to 200	q.s. to 200

*Quantities given for each tablet in mg

Preparation of two layered tablets

Oral controlled release tablets each containing 75 mg of indomethacin were designed as two layered tablets with an immediately releasing layer consisting of solid dispersible indomethacin (50 mg), Ac-Di-Sol(25 mg), Lactose(25 mg) and PVP K-30(0.01 mg) and a matrix consisting of solid dispersible indomethacin (100 mg) in Carbopol 934 LR or Hydroxyl Propyl Cellulose.

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Table No.2 Composition of IR layer tablets (mg)

Ingredients	Quantity(mg)
Solid Dispersible Indomethacin	50
Ac-Di-Sol	25
PVP K-30	0.01
Lactose	q.s. to 100

EVALUATION PARAMETER

Drug content in solid dispersion of indomethacin

The indomethacin dispersion (400 mg) was accurately weighed and transferred to a 250 ml volumetric flask. To this, 150 ml of dilute NaOH solution was added. The flask was shaken to dissolve the powder. Sufficient dilute NaOH solution was added to adjust the volume. An aliquot (10 ml) of this solution was taken and diluted with the NaOH solution to 100 ml. The drug present in the solution was analyzed by spectrophotometrically at 318 nm using shimadzu UV-1800 double-beam spectrophotometer. The drug content was found to be 49.89% (SD± 0.07765) [14].

Weight variation

Twenty tablets were selected at random, weighed and the average weight was calculated. Not more than two of the individual weights should deviate from the average weight by more than 5%. . Note down % weight variation of given tablets which is shown in table III.

Friability

For each formulation, pre weighed tablet sample (20 tablets) were placed in the EF-2 Friabilator USP (electrolab ltd.), which is then operated for 100 revolutions. The tablets were dedusted and reweighed. Conventional compressed tablets that loose < 0.5 to 1% of their weight are considered acceptable. Note down % friability of given tablets which are shown in table III.

Crushing strength

Crushing strength of tablet was determined using Pfizer crushing strength tester. Crushing strength of mucoadhesive oral bilayer tablets were given in the following table III.

Drug content uniformity

Weigh and powdered 20 tablets. Weigh accurately a quantity of the powder equivalent to 75mg of Indomethacin and transferred to a 250 ml volumetric flask. To this, 150 ml of dilute NaOH solution was added. The flask was shaken to dissolve the powder. Sufficient dilute NaOH

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solution was added to adjust the volume. An aliquot (10 ml) of this solution was taken and diluted with the NaOH solution to 100 ml. The drug present in the solution was analyzed by spectrophotometrically at 318 nm using shimadzu UV-1800 double-beam spectrophotometer [14].

Table No.3 Evaluation parameters of prepared formulation (B1 to B9)

Formulation	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Content Uniformity (%)	weight Variation
B1	4.1 ± 0.15	0.11	4.1 ± 0.01	99.89	300.66 ± 1.3
B2	4.2 ± 0.17	0.11	4.1 ± 0.02	100.02	299.96 ± 1.1
B3	4.0 ± 0.16	0.14	4.2 ± 0.01	95.62	295.26 ± 0.3
B4	4.2 ± 0.15	0.13	4.1 ± 0.01	99.92	310.53 ± 1.6
B5	4.4 ± 0.19	0.13	4.4 ± 0.04	99.96	305.45 ± 1.2
B6	5.1 ± 0.14	0.15	4.1 ± 0.02	95.89	302.62 ± 1.8
B7	5.3 ± 0.12	0.11	4.3 ± 0.03	100.2	301.66 ± 1.9
B8	5.8 ± 0.15	0.1	4.1± 0.01	102.1	298.54 ± 1.1
B9	5.6 ± 0.19	0.15	4.4 ± 0.04	100.3	299.37± 1.1

In vitro drug release study of mucoadhesive indomethacin tablets

The in vitro dissolution study were conducted for all formulation using USP dissolution test apparatus Type I, (Electro Lab). Release of indomethacin from mucoadhesive tablets was studied for 12 hrs with the paddle apparatus using 0.1 N HCL. The dissolution study was carried out at 75 rpm and 37±0.5 ^{0}C. Indomethacin was evaluated spectrophotometrically at 318 nm using shimadzu UV-1800 double-beam spectrophotometer. The drug release experiments were conducted in triplicate and the mean values were plotted versus time with standard deviation less than three indicating reproducibility of result. The plot of percentage cumulative drug release against time (Hrs.) is shown in Figure I [15].

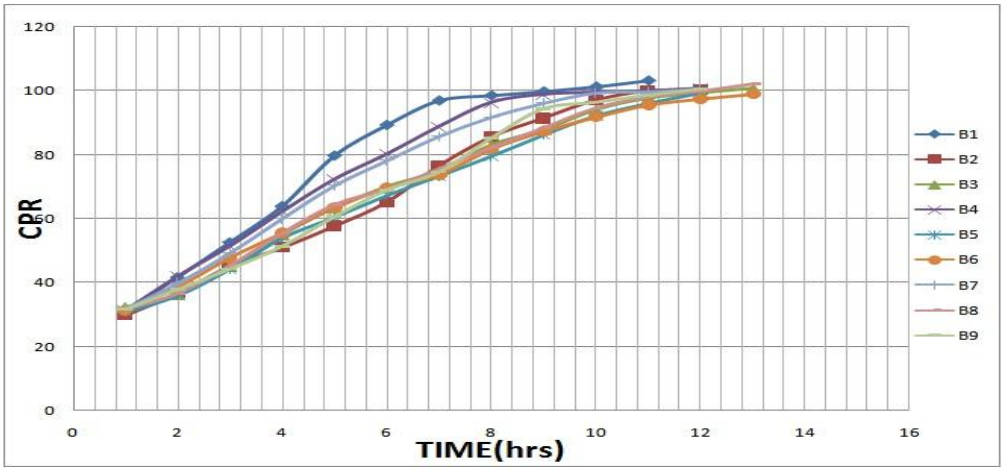

Figure No.1 Dissolution study of mucoadhesive oral bilayer tablets of indomethacin

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Kinetic Model fitting

To determine the release kinetic drug, various mathematical models are applied like Higuchi diffusion model, korsmeyer-peppas model, Hixon-crowell model, zero order model and first order model. Correlation coefficient (R^2) and diffusion coefficient (d) of these models are mentioned in Table IV.

Model	R^2	n	K
Hixon Crowel	-0.97	-	-
Higuchi	0.9952	-	-
First Order	0.9429	-	-
Zero Order	0.9784	-	-
Korsemeyer-Peppas	0.9945	0.486	0.29

Table No.4 Kinetic treatment of the release data from mucoadhesive oral bilayer tablets (B6)

Bioadhesive strength

This study was carried out by simple modified double pan weight balance. One surface of mucoadhesive tablet was stick to bottom surface of one pan of weight balance by sticky gum. Another surface of mucoadhesive tablet was adhered with agar media as mucous membrane in Petri disk. One by one calibrated fractional weight put in another pan until tablet was dispatched from pan of the weight balance and measured the strength of tablet. The bioadhesive strength of different formulated batches and the simple modified weight balance are shown in Figure II & III [16].

Figure No.2 Photography of Simple modified weight balance for bioadhesion study

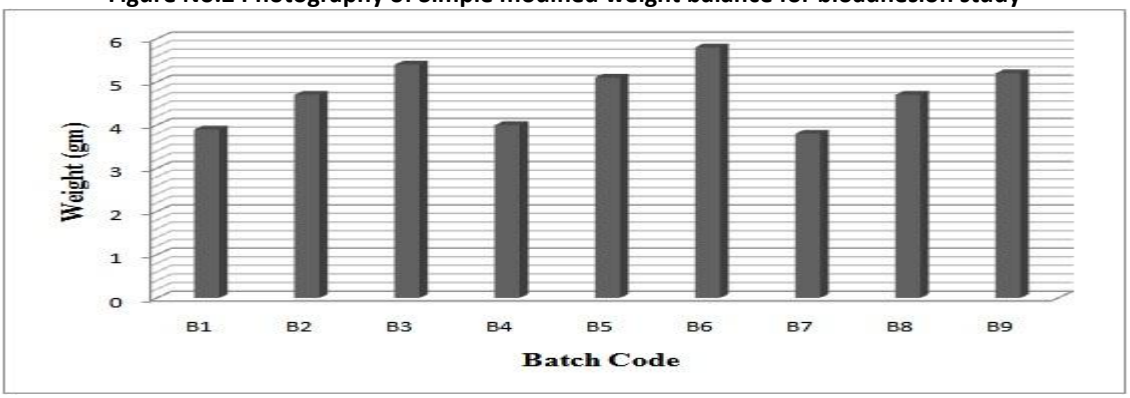

Figure No.3 Comparison of bioadhesive strength for mucoadhesive oral bilayer tablets

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RESULTS AND DISCUSSION

Immediate layer of the prepared mucoadhesive matrix tablets were found to be disintegrating within a minute in water and 0.1 N HCl while Controlled release layer was found to be non-disintegrated. Crushing strength of the tablets was in the range of 4.5-5.5 kg/cm^2. Percentage weight loss in the friability test was less than 0.15 % in all the batches. The tablets in all the batches contained indomethacin within 100±5 % of the labeled content. Not more than 2 tablets were differing from the average weight by more than 5% and not a tablet differs by more than 10%. The tablets of prepared batches were in the limit of crushing strength, friability and drug content, weight variation and disintegration time as per IP 1996 .

Drug release from matrix formulation examined during in vitro dissolution study. At the end of 12 hours, the matrix shape was not changed that indicating the drug released from matrix tablet by diffusion.

Higuchi has described drug release mechanism from matrix dosage forms using the following equation:

$$Q = [D(2W-C_s)\, c_{st}]^{1/2}$$

In the above equation, D is the diffusion co efficient of the drug in the matrix, W is the total amount of the drug per unit volume of the matrix, C_s is the solubility of the drug in the matrix and t is the drug release time. When $W>>C_s$, the above equation can be simplified to the following.

$$Q = [2WDC_{st}]^{1/2}$$

This equation indicates that the amount of drug release is proportional to the square root of time for the diffusional release of a drug from the matrix type system. The linear correlation co efficient of the slope shown in the table IV indicating that the drug release from Carbopol 934 LR and Hydroxy Propyl Cellulose polymeric matrix follows the higuchi diffusion model. It had shown that the concentration of Carbopol 934 LR and Hydroxy Propyl Cellulose increased, the drug release time is extended due to firmness between polymeric particles. To gain some insight into the drug release mechanism, a very simple and semi empirical equation to describe the drug release from the polymeric system, the korsmeyer peppas model was also applied.

$$M_t / M_\infty = K\, t^n$$

A Concentration of Carbopol 934 LR and Hydroxy Propyl Cellulose increased, the bioadhesive strength was increased due to more adhesion between polymer and mucous membrane.

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