FORMULATION AND DEVELOPMENT OF KETOPROFEN BILAYER TABLETS

Available online at www.ijdra.com

RESEARCH ARTICLE

[1]Nagesh D R*, [1]Jat Rakesh Kumar, [2]Ahmed Syed Mansoor

[1]Institute of Pharmacy, Shri JJT University Jhunjhunu (Raj) India.

[2]Sree Siddaganga College of Pharmacy, Tumkuru, Karnataka, India.

Corresponding Author's E-mail: nageshdr29@gmail.com

DOI: https://doi.org/10.22270/ijdra.v5i4.207

ABSTRACT

Aim of present research work was formulation and development of bilayer tablets of Ketoprofen to reduce the side effects of Ketoprofen and to improve the therapeutic benefits and patients' compliance to treatment. Bi-layer tablets of Ketoprofen were prepared by direct compression technique using excipients like MCC, superdisintegrant, aspartame, colour agent were mixed properly shifted from sieve no 40. Before compression; add talc magnesium stearate mixed it well. Formulations with optimal properties have been selected to obtain bi-layer tablets of adequate quality. The in vitro dissolution study of the prepared bilayer tablets showed a controlled release of active drugs over a period of 24 hours.

Keywords: Bilayer Tablets, Ketoprofen, Superdisintegrant.

INTRODUCTION

Oral route is the most commonly employed route of drug administration. Although different Route of administration are used for the delivery of drugs, oral route remain the preferred mode. The popularity of the oral route is attributed patient acceptance, ease of administration, accurate dosing, cost effective manufacturing method and generally improved shelf-life of the product. Even for sustained release systems the oral route of administration has been investigated the most, because of flexibility in dosage forms design that the oral route offers. With many drugs, the basic goal of therapy is to achieve a steady-state blood level or tissue level that is therapeutically effective and non-toxic for an extended period of time. (1-3)

Bi-layer tablet concept has long been utilized to develop sustained released formulation. Such tablet has a fast releasing layer and may contain one (bi-layer), to sustain the drug release. The pharmacokinetic advantage relies on the criterion that, drug release from the fast releasing layer leads to a sudden rise in the blood concentration. However the blood level is maintained at steady state as the release from sustaining layer. (4-6)

Bi-layer tablet is sensible for dynamic passage of two medicines in mix, separate two contradicting substances other than for kept up discharge tablet in which one layer is energetic discharge as beginning estimations second layer is reinforce estimation. This bilayer approach is a convenient method. Hence it makes possible to formulate sustained release preparations with the immediate release quantity in one layer and the slow release portion will disintegrate rapidly after ingestion thus providing the Initial dose of medication for immediate onset of action, whereas the another layer in the matrix layer remain intact during most of the time of its passage through the intestine, While dissolving slowly (sustained manner) from its exposed faces in this passage, which helps to maintain the blood level initially reached.

METHODOLOGY

Pre-formulation study

Organoleptic Characteristics of Ketoprofen

Physical examine was done to check Organoleptic Characteristics of Ketoprofen like color and odor.

Determination of λ_{max} and Preparation Calibration Curve

100 mg of pure Ketoprofen was dissolved in 100 ml of pH 6.8 phosphate buffer. 1 ml of this solution was pipette out in separate 10ml volumetric flask diluted suitable media subjected to UV scanning in range 200 - 400 nm using double beam UV - visible spectrophotometer.

Solubility study of Ketoprofen

Preformulation solubility analysis will be done, which included dissolving drug with excess quantity in glass vials containing 20mL suitable solvent system supernatant solution will be filtered using 0.45 µm pore size filter after 24 hrs at room temperature. First 10 mL of filtrate was discarded last portion of filtrate was suitably diluted with water assayed spectroscopically at 376nm. Procedure was followed by using different solvents like water, ethanol, methanol, DCM, DMSO.

Drug–excipients compatibility Studies by FTIR

IR spectroscopy will conducted using FTIR Spectrophotometer spectrum was recorded in wavelength region of 400–4000 cm^{-1}.

Preparation of Ketoprofen Bilayer Tablets

Preparation of Sustained Release Layer

Ketoprofen sustain release layer had been formulated by utilizing direct compression procedure. Weighed quantities of desired weighed of solid medicament other excipients like MCC, Retardant polymer were mixed properly shifted from sieve no 40. Before compression adds talc magnesium stearate mixed it well. Prepared powder blended than punched by using single punch tablet compression machine.

Method of Preparation of Immediate release Layer

Ketoprofen Orodispersible layer were prepared by using direct compression method. Desired quantities already weighed material and other excipients like MCC, superdisintegrant, aspartame, colour agent were mixed properlyshifted from sieve no 40. Before compression; add talc magnesium stearate mixed it well. Prepared powder blended than punched by using single punch tablet compression machine.

Drug Content Uniformity

Ten Tablets were finely powdered and an amount equivalent to 40 mg of Ketoprofen was accurately weighed and transferred to a 100 ml volumetric flask. Then 70 ml methanol was added. The flask was shaken for 10 minutes. Finally, the volume was made up to the mark with methanol. The mixture was then filtered and 1 ml of the filtrate was suitably diluted with methanol to obtain a solution containing about 40 µg ml^{-1} of Ketoprofen and analyzed for Ketoprofen content at 260 nm using a double beam UV/Visible and methanol as a blank.

In-vitro Drug Release Study of Ketoprofen Bilayer Tablets

Release of Ketoprofen was determined using a USP, six stage dissolution rate test apparatus- I at 50 rpm. The dissolution was studied using 900 mL of simulated intestinal fluid (without enzyme pH 6.8). The temperature was maintained at 37±0.5^{0}C. The sample (5ml) was withdrawn at different time intervals i.e.1,2,3,4,5,6,7,8,9,10,11,12 hrs filter through whatman filter paper and replaced by an equal volume of dissolution medium sample were suitably diluted and analyzed for Ketoprofen content at 290 nm.

RESULT AND DISCUSSION

Pre-formulation Study for Ketoprofen (7)

Pre-formulation parameters such as Organoleptic characteristic study, solubility study, Wavelength (λ_{max}) Determination, Calibration curve, Identification of Drug by FT-IR study was carried out.

Organoleptic characteristics of Ketoprofen

Physical examine was done to check Organoleptic Characteristics of Ketoprofen like color, odor physical appearance of pure drug.

Table 1: Organoleptic parameters

Parameter	Observation
Colour	White
Odour	Odour less

Appearance	White Powder

Determination of solubility of Ketoprofen

Solubility of Ketoprofen drug was carried out with help of different solvent. Result shows solubility of drug near about 1mg in 10ml of solvents.

Table 2: Solubility of Ketoprofen

S. No.	Solvent	Concentration (mg/ml) n=3(±SD)	Parts of solvent required for part of solute
1	Water	0.002±0.001	From 1 to 10
2	Ethanol	0.046±0.003	From 1 to 10
3	0.1N HCL	0.034±0.004	From 1 to 10
4	7.4 Phosphate buffer	0.032±0.003	From 1 to 10
5	6.8 Phosphate buffer	0.037±0.002	From 1 to 10

Calibration curve of Ketoprofen

λmax of sample was found to be 260 nm.

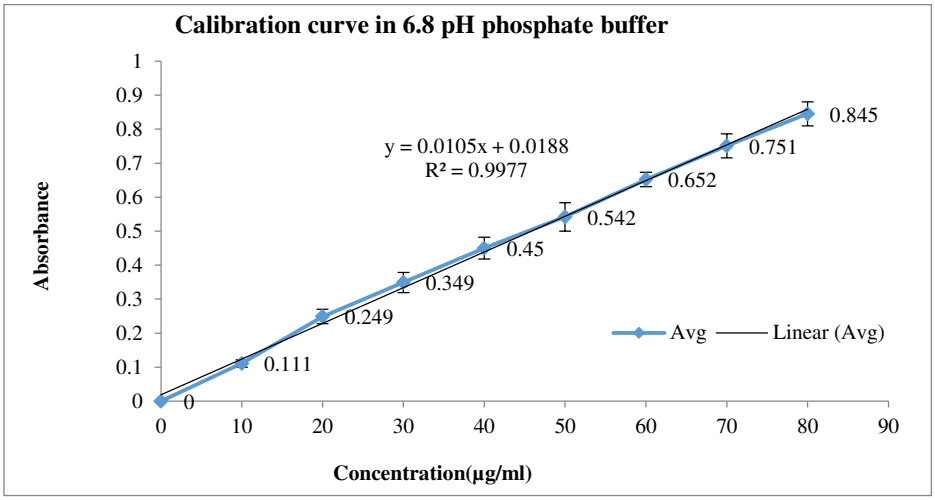

Figure 1: Calibration curve for Ketoprofen

Identification of Drug by FT-IRDSC study

a) By FTIR spectroscopy

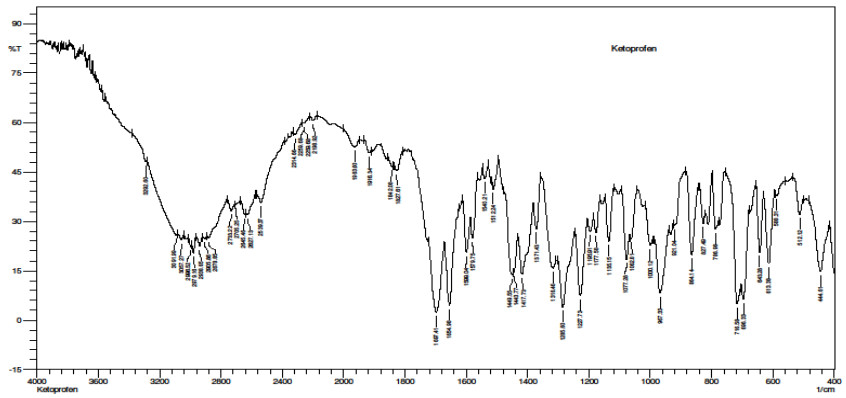

Figure 2: FT-IR spectra for Ketoprofen

Interpretation of pure drug

Table 3: IR interpretation data of spectrum for Ketoprofen

Inference	Standard wave number(cm^{-1})	Observed wave number(cm^{-1})	Interpretation
-C=O Stretching	1600-1900	1667.41	Observed wave number within standard limit which indicates no interaction.
-CH_3 Stretching	2850-2960	2879.70	
-C=C Stretching	2100-2650	2345.51	
-CH Stretching	600-900	710.50	

From observation of FTIR spectrum is shows that there was no significant difference in wave number of different functional group present in graph. So it could be said that test sample is of Ketoprofen.

Drug- Excipients compatibility study by FTIR spectroscopy

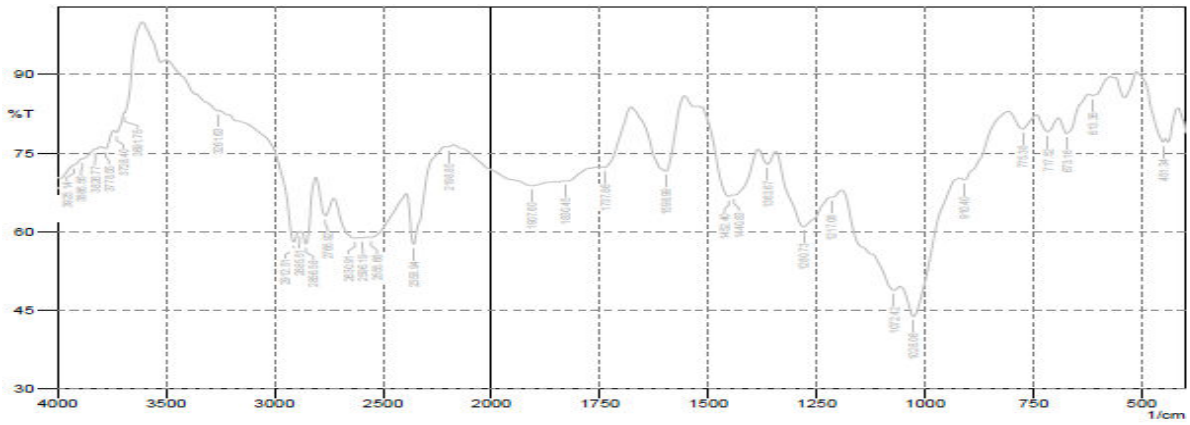

Figure 3: FT-IR spectra for Ketoprofen + All excipients

Table 4: IR interpretation data of spectrum for Ketoprofen + All excipients

Inference	Standard wave number(cm^{-1})	Observed wave number(cm^{-1})	Interpretation
-C=O Stretching	1600-1900	1737.86	Observed wave number within standard limit which indicates no interaction
-CH_3 Stretching	2850-2960	2885.51	
-C=C Stretching	2100-2650	2698.85	
-CH Stretching	600-900	613.36	

From observation of FTIR spectrum is showed that there was no significant difference in wave number of different functional group present in sample. So it could be said that test sample of Ketoprofen other ingredients mixture shows no interaction between each other.

Preliminary Selection of Type of retardant Material for Ketoprofen sustained Release layer (8):

Table 5: Composition of proposed trial batches of Ketoprofen tablets

Tablet composition	Weight (mg)
Ketoprofen	10
Retardant material	25-75%
MCC	42.2
Talc	3
Magnesium Stearate	2

Table 6: Preliminary Selection of Type of Retardant Material for Ketoprofen sustained Release layer.

Batch	Type of retardant material	Concentration of Retardant material
KTPB1	Ethyl Cellulose	50
KTPB2	HPMC K4M	50
KTPB3	HPMC K100M	50
KTPB4	Eudragit	50
KTPB5	Polyox WSR 303	50

Characterization of Preliminary trial Batches (KTPB1-KTP5) (8-10)

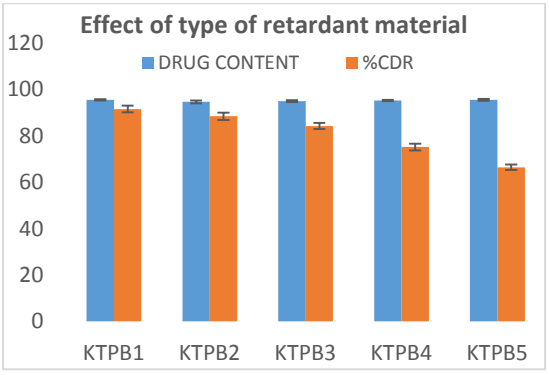

Figure 4: Effect of type of retardant material

Sustained release drug delivery system required polymers which having property to sustained release of dreg when it is incorporated in to formulation. Retardant polymer such as HPMC, Chitosan, Eudragit, Polyox etc. is used in pharmaceutical formulation to sustain drug release. However, concentration of retardant polymer in sustained release tablets must be optimum. Here, Polyox 303 has been found to be very effective retardant polymer for sustained release tablet produced by various methods. Retardant polymer having property of swelling and gelling by which they controlled the release of drug from the formulation. In fact, effectiveness of Polyox 303 in sustaining drug release is such that it even controls drug release without interfering with drug content. Even retardant; polymer like HPMC eudragit have been utilized for reducing drug release from tablet. Hence, LSB3, LSB4LSB 5 have been selected as optimized batches.

Preliminary Selection of Concentration of Retardant Material

Table 7: Preliminary Selection of Concentration of Retardant Martial on Ketoprofen sustained Release layer.

Batch	Type of retardant material	Concentration of Retardant material
KTPB6	HPMC K100M	25
KTPB7	HPMC K100M	50
KTPB8	HPMC K100M	75
KTPB9	HPMC K100M	100
KTPB10	Eudragit	25
KTPB11	Eudragit	50
KTPB12	Eudragit	75
KTPB13	Eudragit	100
KTPB14	Polyox WSR 303	25
KTPB15	Polyox WSR 303	50
KTPB16	Polyox WSR 303	75
KTPB17	Polyox WSR 303	100

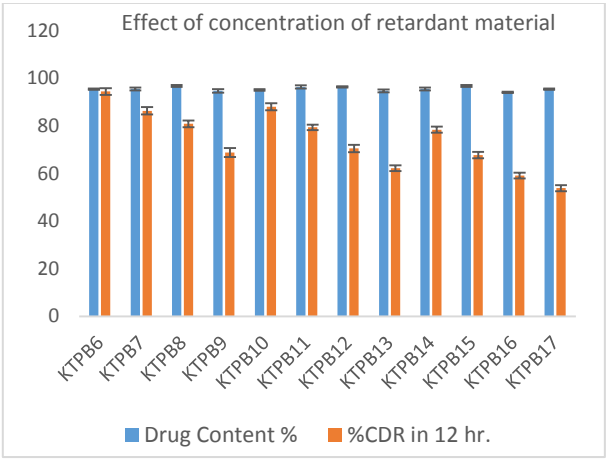

Figure 5: Effect of concentration of retardant material on drug content and drug release

As retardant material is basic requirement for formulation of sustained release formulation. To enhance sustain release, formulation need high concentration of retardant material. As per preliminary trial batches, as concentration of retardant material increase, sustaining release of drug increase. Therefore, 100 mg of retardant material selected as maximum concentration for formulation of sustained release layer.

Preliminary Trial Batches for Orodispersible Layer

Preliminary Selection of Type of Super Disintegrants

Table 8: Preliminary Selection of Type of Super Disintegrants

Batch	Type of Super Disintegrants	Concentration of Super Disintegrants
KPOB1	Sodium Starch Glycolate	10
KPOB2	Cross Povidone	10
KPOB3	Cross Carmalose Sodium	10
KPOB4	Kyron 314	10

Characterization of Trial batches (KPOB1-KPOB4)

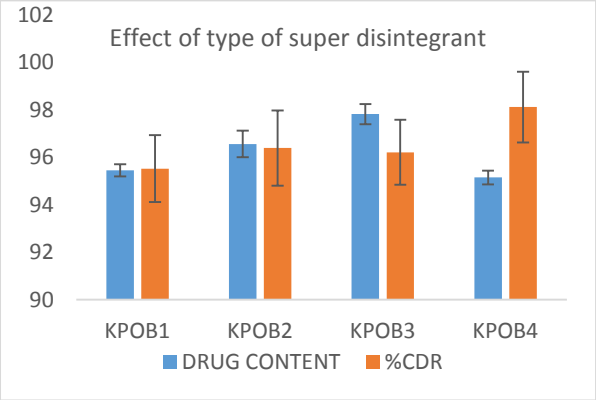

Figure 6: Effect of type of superdisintegrant on % drug content and drug release

Orodispersible drug delivery system required super disintegrants which has property to rapid release of drug when it is incorporated in to formulation. Super disintegrants such as Sodium starch glycolate, cross povidone, cross Carmalose sodium Kyron 314 are used in pharmaceutical formulation for immediate drug release. However, concentration of super disintegrants in immediate release tablets must be optimum. Here, Kyron 314 has been found to be very effective super disintegrants for immediate release tablet produced by various methods. Super disintegrants having property of pore forming higher water absorptivity by which they increase release of drug from formulation. Even super disintegrants like cross povidone cross Carmalose sodium have been utilized for enhance drug release from tablet. Hence, KPOB2, KPOB3KPOB5 have been selected as optimized batches.

In-vitro disintegration Study

In-vitro disintegration study is important to identify disintegration time. As fast tablet disintegrate, gives faster release.

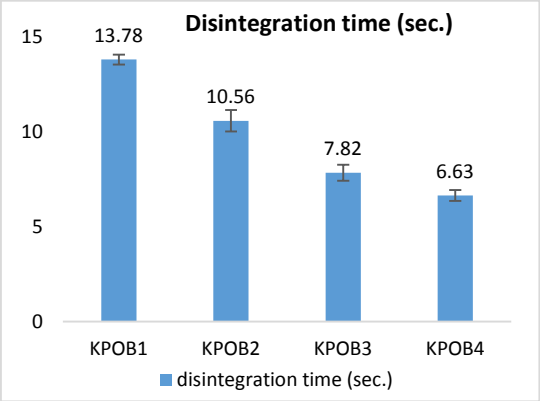

Figure 7: In-vitro disintegration study

CONCLUSION

Present investigation was finished to develop bilayer tablet of Ketoprofen using superdisintegrant Kyron 314 for snappy release layer Polyox 303 for supporting release layer. Tablets exhibited fundamental burst release to give stacking estimation of pharmaceutical took after by kept up release up to 24 hrs. This balanced release bilayer tablets moreover diminished dosing repeat, manufacture bioavailability give better patient consistence.

Bi-layer tablet is upgraded valuable development to vanquish obstruction of single layered tablet. It is proper for progressive entry of medicines for bolstered release tablet in which one layer is snappy release as starting dose second layer is upkeep estimations. Course of action of tablets as multi layers is used to offer structures to association of meds, which are opposite to give controlled release tablet game plans by giving incorporating or various swelling layers.

ACKNOWLEDGEMENTS

The authors are thankful to IJDRA journal for publishing our article.

CONFILCTS OF INTEREST

The authors declare that there are no conflicts of interest.

REFERENCES

1. Jha MK, Rahman MH and Rahman MM. "Biphasic oral solid drug delivery system: a review." Int. J. Pharm Sci and Res. 2011; 2: 1108-15.
2. Saravanan V, Revathi R, Meera N. Method development and validation for the simultaneous estimation of lycopene and ubidecarenone by RP-HPLC in combined pharmaceutical dosage form. Journal of Drug Delivery and Therapeutics. 2016; 6(5): 46-51.
3. Abebe A, Akseli I, Sprockel O, Kottala N, and Cuitino AM. "Review of Bilayer Tablet Technology." International. J. Pharmaceutics. 2014; 461:549-58.
4. Dagariya RK, Jat RK. Method development and validation of Irbesartan chlorthalidone and Cilnidipine in their combined tablet dosage form by high performance liquid chromatography. Journal of Drug Delivery and Therapeutics. 2017; 7(4):88-96. doi: http://dx.doi.org/10.22270/jddt.v7i4.1471
5. Kumar AP, Pramodaganta, Bhoopathi SG and, Kulkarni SV. "Current Innovation in Layered Tablet Technology: Review." Asian. J. Res pharm. sci.; 2013: 3:189-94.
6. Garg A, Gupta MM. Taste masking and formulation development & evaluation of mouth dissolving tablets of levocetrizine dihydrochloride. Journal of Drug Delivery & Therapeutics. 2013; 3(3):123-130.
7. Momin S, Khan S, Ghadage DM, Yadav AV, Wagh A. Formulation and evaluation of bilayer tablets of propranolol hydrochloride. Journal of Drug Delivery and Therapeutics. 2017; 7(2):50-57. doi: http://dx.doi.org/10.22270/jddt.v7i2.1399
8. Debajyoti Ray, Amresh K Prusty. Designing and in-vitro studies of gastric floating Tablets of Tramadol hydrochloride. Int J Appl Pharm. 2010; 2(4):12-16.
9. Patel K, Vyas J, Upadhyay U. Formulation and evaluation of sustained release matrix tablets of nateglinide. Journal of Drug Delivery and Therapeutics. 2015; 5(5):19-25. doi:10.22270/jddt.v5i5.1130
10. Agrawal R. Pharmaceutical processing- a review on wet granulation technology. IJPFR. 2011; (1):65-83.

