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STUDIES ON NATURAL AND SYNTHETIC POLYMERS FOR CONTROLLED RELEASE MATRIX TABLET OF ACECLOFENAC

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Abstract:

The present study was aimed to design new oral controlled release matrix tablets of new NSAID Aceclofenac for once a day by using 10, 15, 20 and 25% of GG:HPMC and XG:HPMC mixture in the ratio 1:1 by wet granulation method. The prepared tablets subjected to in vitro drug release studies in pH 7.4 buffer solution. All the formulation meets the pre-compression and compression characteristics. All the tablets prepared with 10, 15, 20 and 25% of HPMC: XG mixture in the ratio 1:1 fails to meet the requirement of complete release of the drug in 24h. The tablet formulations containing 10% and 15% of GG: HPMC mixture fails to control release of drug upto 24h. The formulation AHG20 controlled release of drug upto 24h and released more than 97% of the drug in 24h. Hence considered as the best formulation. The optimized tablet batch formulations AHG20 showed no change in drug content or in vitro release pattern after storage at 40° C / 75% RH for 30 days. The FTIR studies indicated absence of interaction between aceclofenac and tablet excipients used in the matrix tablets. It has been observed from the above study that excipients like HPMC, xanthan gum, guar gum and microcrystalline cellulose were ideal excipients and effective for formulating controlled release matrix tablets. As these excipients are easily available, inexpensive and compatible. Controlled release matrix tablets provide several advantages reduce dose related toxicity, reduce drug waste and improve patient compliance.

Keywords: *Aceclofenac, guar gum, xanthan gum, CDDS and matrix tablets.*

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INTRODUCTION:

The goal behind the development of controlled drug delivery system is to deliver the drug at a predetermined rate, for locally or systemically, for a specified period of time. Continuous oral delivery of drugs at predictable and reproducible kinetics for predetermined period throughout the course of GIT [1]. Controlled release drug delivery employs drug-encapsulating devices from which therapeutic agents may be released at controlled rates for long periods of time, ranging from days to months. Such systems offer numerous advantages over traditional methods of drug delivery, including tailoring of drug release rates, protection of fragile drugs and increased patient comfort and compliance [1-3]. Oral route is the most widely preferred route for drug administration due to its safety, ease of administration and patient compliance. Various approaches have been introduced for the controlled release of drug after the oral administration [4,5]. Non-steroidal anti-inflammatory drugs (NSAIDs) are considered to be the first line drugs in the symptomatic treatment of rheumatoid arthritis, arthritis, osteoarthritis and spondylitis. Aceclofenac, is a newer derivative related to Diclofenac, is widely used non steroidal anti-inflammatory drug (NSAID) with low gastrointestinal complications [6]. The short biological half-life (3- 4h) and dosing Frequency more than one per day makes aceclofenac an ideal candidate for controlled sustained release. To minimize the gastrointestinal disturbances such as peptic ulceration with bleeding to reduce the frequency of administration and to improv e patient compliance, a once in a day controlled release formulation of aceclofenac is desirable [7]. Therefore, in the present work it was planned to formulate a controlled release matrix tablets of aceclofenac by using xanthan gum along with HPMC as tablet matrix formers [8]. The major objectives of the investigation are to develop simple analytical method for quantitative estimation of drug by preparation of calibration curve of model drug aceclofenac in pH 1.2 and pH 6.8 buffer solutions. To perform drug-excipient compatibility studies by FTIR spectroscopy. To study flow properties of powder bed (ready for compression) materials like angle of repose and Carr's compressibility index. Preparation of aceclofenac controlled release matrix tablets by wet granulation technique by using natural polymer like guar gum and xanthun gum along with HPMCK_4M [9]. To evaluate aceclofenac controlled release matrix tablet for various in process quality control tests like thickness, hardness, friability, weight variation etc.

MATERIALS AND METHODS:

Materials:

Aceclofenac was a gift sample form Arvind Remedies Ltd, Tamil Nadu, India. Polymers used like Xanthan gum, Guar gum, Microcrystalline Cellulose, Talc, HPMC.

Methods:

Drug-Excepients Compatibility Studies by FTIR

Infra Red spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug. The pure drug and its formulation were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed.

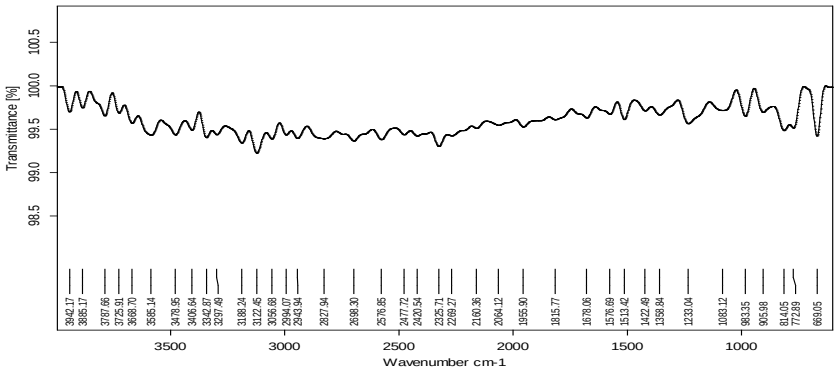

Fig. 1: FTIR spectra of pure powdered drug aceclofenac.

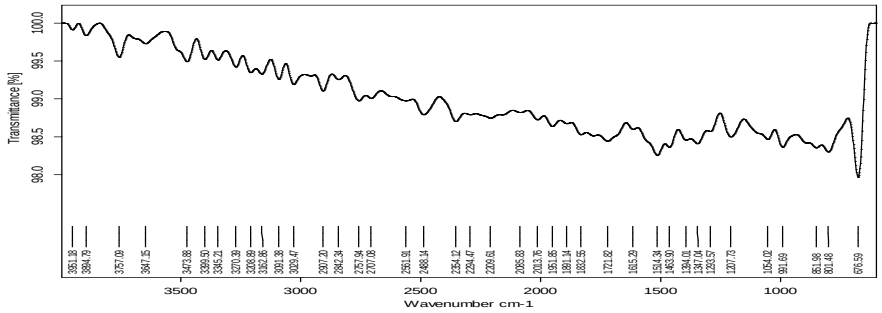

Fig. 2: FTIR spectra of controlled release matrix tablet powder mixture formulation.

Fig. 3: FTIR spectra of controlled release matrix tablet powder mixture formulation AHG20.

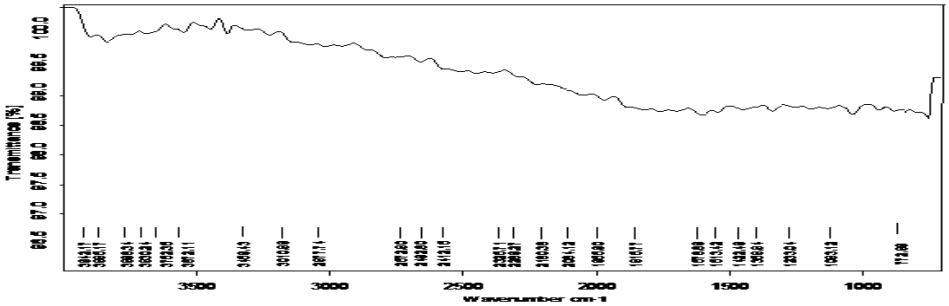

Fig. 4: FTIR spectra of powdered placebo tablet formulation AHG20

Flow Properties Measurement:

The aceclofenac powder material prepared by direct powder mixing technique were evaluated for various rheological properties like bulk density, tapped density, compressibility index, flow properties (angle of repose) by using standard procedures. All studies were carried out in triplicate (n=3) and average values were reported.

Table No. 1: Flow properties of controlled release matrix tablet powder formulations.

Formulation Codes	Angle of Repose (θ)	Carr's Index (%)
AHG10	28.09^0	13.28
AHG15	28.84^0	15.63
AHG20	23.84^0	12.37
AHG25	28.39^0	13.44
AHX10	24.87^0	13.52
AHX15	29.34^0	14.57
AHX20	28.84^0	15.82
AHX25	23.82^0	14.93
AHG20 (250)	27.53^0	15.28

**All values are mean (n=3) ± SD*

Preparation of Aceclofenac Controlled Release Matrix Tablets:

Controlled release matrix tablets containing aceclofenac were prepared by wet granulation technique by using 5% w/v starch paste as binding agent. The composition of HPMC, Xanthum gum and Guar gum are given in table 2. All the powder ingredients like aceclofenac, MCC, HPMC, GG/XG were taken in a clean mortar and powdered them with pestle and passed through sieve no 44 to remove any lumps. Then sufficient amount of starch paste was added to prepare soft wet mass. The resulting wet mass is passed through sieve 12 to get wet granules. The wet granules dried in an hot air oven at 600C for 40-45 min. The dry granules regranulated by passing through sieve 12/44. The granules and fines collected and weighed separately. The granules were then mixed with 10% fines, talc and magnesium stearate to make granules ready for compression. The granules were then compressed by using 9mm flat plain single punch tablet machine. The formulae of different tablet formulation used for preparation of tablet were shown in table 2.

Table No. 2. Composition of Controlled Release Matrix Tablets Containing Aceclofenac.

Ingredient (mg)	**Category**	**Composition of aceclofenac controlled relaese matrix Tablet**								
		AHX10	AHX20	**AHX30**	**AHG40**	**AHG10**	**AHG20**	**AHG30**	**AHG40**	**AHG20 (LD)**
Aceclofenac	Active drug	200	200	**200**	200	200	200	200	200	250
HPMC K4M	Hydrophilic	20	30	40	50	20	30	**40**	50	30
Xanthan gum	Release modifier	20	30	40	50	--	--	--	--	--
Guar gum	Release modifier	--	--	--	--	20	30	**40**	50	30
Starch paste (5%)	Binding Agent	24	24	24	24	24	24	**24**	24	24
MCC	Diluents	128	108	88	68	128	108	**88**	68	68
Talc	Lubricant	4	4	4	4	4	4	**4**	4	4
Mag.stearate	Glidant	4	4	4	4	4	4	**4**	4	4
HPMC:XG	----	1:2	1:3	1:4	1:5	1:2	1:3	**1:4**	1:5	1:3
Total weight (mg)		400	400	400	400	400	400	**400**	400	400

Compression characteristics of tablets:

Table No. 3. Compression characteristics of aceclofenac controlled release matrix tablets.

Formulation Codes	Diameter (mm± SD)	Thickness* (mm± SD)	Hardness* (Kg/cm^2± SD)	Friability (%)	Drug Content* (%± SD)	Weight Variation (%)
AHG10	9.04 ± 0.11	4.45 ± 0.05	5.15 ± 0.27	0.397	99.59 ± 4.56	1.651
AHG15	9.01 ± 0.10	4.41 ± 0.11	5.31 ± 0.16	0.633	99.63 ± 3.64	3.258
AHG20	9.01 ± 0.12	4.46 ± 0.09	5.16 ± 0.11	0.239	99.96 ± 4.65	2.754
AHG25	9.00 ± 0.12	4.59 ± 0.12	5.20 ± 0.21	0.515	98.09 ± 2.56	2.712
AHX10	9.03 ± 0.06	4.59 ± 0.04	5.12 ± 0.11	0.397	96.46 ± 3.91	2.246
AHX15	9.06 ± 0.12	4.66 ± 0.16	5.15 ± 0.33	0.520	98.49 ± 1.21	3.753
AHX20	9.04 ± 0.02	4.54 ± 0.14	5.12 ± 0.16	0.336	97.36 ± 4.17	2.057
AHX25	9.05 ± 0.11	4.70 ± 0.10	5.30 ± 0.27	0.359	96.35 ± 4.35	1.895
AHG20(LD)	9.03 ± 0.34	4.85 ± 0.09	5.04 ± 0.33	0.458	98.87 ± 3.24	3.845

All values are mean (n=5) ± SD

***in vitro* drug release studies:**

Table No. 4: In vitro release data of aceclofenac from controlled release matrix tablet formulations containing HPMC: GG

Sr. No.	Time	Percent Aceclofenac Released			
		AHG10	AHG15	AHG20	AHG25
1	0	0	0.00	0.00	0.00
2	1	10.12	8.21	7.31	5.24
3	3	18.65	16.32	14.21	13.32
4	5	29.53	25.36	26.36	24.92
5	8	48.65	42.38	35.67	32.98
6	10	63.27	58.61	45.68	41.28
7	12	78.92	65.71	52.36	49.3
8	15	98.23	79.23	68.32	63.32
9	18	---	91.25	76.85	72.21
10	21	---	99.84	88.95	85.23
11	24	---	---	97.25	93.58

All values are average of three readings.

Table No. 5: In vitro release data of aceclofenac from controlled release matrix tablet formulations containing HPMC & XG.

Sr. No.	Time in hour	Percent Aceclofenac Released			
		AHX10	AHX15	AHX20	AHX25
1	0	0.00	0.00	0.00	0.00
2	1	9.11	7.15	6.73	5.28
3	3	17.08	16.32	15.08	13.62
4	5	25.34	22.92	20.67	19.56
5	8	36.28	29.39	27.38	24.38
6	10	44.12	37.52	32.57	31.63
7	12	58.92	45.69	41.28	38.63
8	15	67.18	55.98	49.62	45.81
9	18	75.28	64.08	57.06	54.9
10	21	82.16	73.39	67.28	65.27
11	24	89.34	83.09	78.39	75.74

All values are average of three readings.

Table No.6: Effect of loading dose on release of aceclofenac from optimized batch formulation AHG20.

Sr. No.	Time (H)	Percent Aceclofenac Released	
		AHG20 (200)	AHG20 (250)
1	0	0.00	0.00
2	1	7.31	8.68
3	3	14.21	17.32
4	5	26.36	28.94
5	8	35.67	36.67
6	10	45.68	49.21
7	12	52.36	56.32
8	15	68.32	72.64
9	18	76.85	77.34
10	21	88.95	92.31
11	24	97.25	98.63

Table No.7: Stability data of optimized batch formulation AHG20 before and after storage at 40°C / 75% RH for 30 days.

Formulation Code	Thickness (mm)	Thickness* (mm± SD)	Hardness* (Kg/cm^2± SD)	Friability (%)	Drug Content* (% ± SD)	Weight Variation (%)
AHG20 (BS)	9.01 ± 0.12	4.46 ± 0.09	5.16 ± 0.11	0.239	99.96 ± 5.65	2.754
AHG20 (AS)	9.03 ± 0.48	4.52 ± 0.27	5.26 ± 1.84	0.425	98.36 ± 0.27	2.127

RESULT& DISCUSSION

The powder bed material which is ready for compression were tested for their flow properties by determining repose angle (Θ), bulk density (gm/ml), tapped density (gm/ml), and compressibility index (%), by adopting standard techniques, The values obtained for angle of repose for all the formulations are tabulated in Table 3. The values were found to be

in the range of 23.840 to 28.840. This indicates that the powder materials have good flow property. The tapped and untapped density of all the formulation was less than 1. Study of powder rheology indicated a Carr's compressibility index of less than 16 % and therefore it was ascertained that, the powder bed is compressible indicating that the granules have the required flow property for compression. Microscopic examination of the tablets of all the batches reveals no cracks or lines on the surface of the tablet. Tablets mean thicknesses & diameter were found to be in the range of 4.41 ± 0.11 to 4.85 ± 0.09 mm and 9.01 ± 0.10 to 9.05.11 ± 0.11 mm respectively for all the developed controlled release matrix tablet formulations with an average weight of 400 mg. The thickness & diameter of the tablets was found to be uniform and consistent as indicated by their low SD values in all the batches.

The aceclofenac Controlled Release Matrix tablets of different formulations were evaluated for various physicochemical parameters like weight variation, friability, tablet strength (hardness & and friability) and the average values were shown in table 3. In a weight variation test, the average percentage deviation of all batches of the tablets was found to be 1.651 to 3.845 % & within the pharmacopoeial limit, hence all compressed tablets passed the test for uniformity of weight as per official requirements. All the tablet formulation showed a hardness value in the range of 5.12 ± 0.11 to 5.30 ± 0.27 kg/cm2 indicating that tablets are of sufficient strength with withstand the mechanical shock during transportation and handling. Tablet hardness is not an absolute indicator of strength. Another measure of tablet's strength is friability. The compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the percentage friability of tablet formulations were found to be in the range of 0.397 to 0.633 % (less than 1%), indicating that the friability is within the limits. Hence, it was understood that the tablets are of sufficient strength to withstand the stress of transportation. All the aceclofenac Controlled Release Matrix tablets showed acceptable properties and complied within specification for weight variation, hardness and friability .Good drug content uniformity in all the compression coated tablet formulation was observed among different batches of the tablets and the percent drug content was found to be in the range of 96.35 ± 4.35 to 99.59 ± 4.56% .This ensures that all the formulations contains stated or labeled or claimed amount of aceclofenac in the tablets.

The compatibility between aceclofenac and excipients in controlled release matrix tablet formulation was assessed by FTIR studies. The FTIR graphs of the neat drug aceclofenac showed absorption peaks at 3342 and 3297 that these broad peaks may be due to OH hydrogen bonding. 2994 is NH aromatic stretching; peaks near 2827 including 2698 may be due to CH stretching of CH2 groups, carbonyl group vibration at 1815 and 1678. Peaks at 1576 and 1513 indicate the presence of C=C ring stretching. The tablet formulation AHG20 (before & after storage) & placebo formulation as shown in Figure 19, 20, 21 & 22 respectively. In case of aceclofenac tablet formulation AHG20 before storage all the bands that are observed for aceclofenac in IR spectra of figure 19 have again appeared, indicating the absence of chemical interaction between aceclofenac and polymers and other tablet excipients. The present research work was aimed to design a novel controlled release matrix tablets for an oral NSAID agent aceclofenac for safe and effective management of arthritis by using GG, XG and HPMC as hydrophilic matrix forming agent. XG and GG were selected as gelling agents as they impart integrity to the tablets and they also work as drug release modifiers. Both the polymers are insoluble in pH 1.2 but swells which helps in retarding the drug release. The results of the in vitro drug release studies carried out on aceclofenac matrix tablets prepared with HPMC, XG, GG and their combinations in different proportions are shown in figures. The ability of the matrix tablets to control and to sustain the drug release upto 24h was assessed by conducting drug release in the physiological environment of stomach (pH 1.2) for 2h and then continued in pH 7.4 upto 24h.

Since natural gums are more cost effective and safer, two natural gums were also used to prepare matrix tablets. Different studies have been reported on the use of these two gums for the preparation of matrix tablets by the direct compression method. Their compaction and flowability properties have found to be suitable for direct compression. A study has shown that the overall compaction characteristics of xanthan gum is quite similar to HPMC and xanthan gum is more readily flowable than HPMC. The controlled release matrix tablets formulations AHG10, AHG15, AHG20 and AHG25 containing GG and HPMC in the ratio 1:1 released 98.23%, 99.84%, 97.25% and 93.58% respectively. The matrix tablet formulations AHG10 and AHG15 released majority of drug within 15 h and failed to control drug release upto 24h.

From the release profile it is evident that the control of release of aceclofenac from the matrix tablet formulation depends upon concentration of HPMC:GG mixture. As the proportion of GG:HPMC mixture increases in the matrix tablet formulations the control of drug release also increases. The formulations AHG10, AHG15, AHG20 and AHG25 controlled the release of aceclofenac for 15, 21, 24, 24h, respectively. The addition of GG to non-ionic cellulose like HPMC increases the viscosity and controls the drug release for an extended time period. Further, there was no marked difference in the release profile of aceclofenac from formulation containing 20% (AHG20) and 25% (AHG25) of GG and HPMC mixture as reported by Muhammad et al. The matrix tablets containing GG and HPMC mixture take up water on contact with the dissolution medium, thus allowing the dissolution of a certain percent of the drug found at and near the tablet surface prior to gel or viscous medium formation. This is followed by hydration and swelling of the polymer, creating porous pathways that could lead to an initial burst release. Tablet swelling was directly correlated with the level of the gum in different formulations. Increasing the level of polymer in the formulation can further sustain the release of the drug, apparently due to a thicker gel or a more viscous region. The gel or viscous aqueous region inhibits further entry of release medium due to its high water content. With time, the diffusion path length increases, resulting in slower drug release. With sufficient viscosity, the gel or viscous region can resist erosion Muhammad et al. Polymer erosion also plays a major role in releasing drug from these matrices (20). These considerations indicate that hydrophilic polymers have the potential to sustain the release of drug from matrix tablets.

A similar study on controlled release matrix tablets containing were prepared by using 10%, 15%, 20% and 25% of XG: HPMC mixture in the ratio 1:1. Xanthan gum is a polymer with high retarding effect, the controlled release matrix tablets formulations AHX15, AHX15, AHX20 and AHX25 containing XG and HPMC in the ratio 1:1 released 89.34%, 83.09%, 78.39% and 75.74% of aceclofenac at the end of 24h respectively .

The formulation AHX20 and AHX25 containing 20% and 25% of HPMC: XG mixture released only around 78% and 75% of the drug at the end of 24h. By reducing the proportion of XG:HPMC polymer mixture in tablets, the drug release was increased and a faster release was observed, however, this did not fulfill the characteristics of an optimized controlled-release formulation, as the release was still low or incomplete (< 90%) during the testing period of 24h.

In comparison with matrix tablets of GG:HPMC, the drug release rate of XG:HPMC tablets is incomplete or low, which is due to the lower drug diffusivity out of the XG:HPMC gel than the GG:HPMC gel. Furthermore, XG:HPMC can produce much more viscous gels than the GG:HPMC. All the formulations composed of XG and HPMC fails to meet the requirements of complete drug release in 24h.

Whereas the formulation AHG20 composed of 20% GG and HPMC mixture in the ratio 1:1 met the desired requirement and controlled drug release up to 24h. Therefore, the formulation AHG20 was considered as the one of the best optimized controlled release matrix tablet formulation. Further, the formulation AHG20 was prepared with 250 of drug aceclofenac (AHG20(250)) to study the effect of loading dose on the drug release rate. From the study, it is evident that the percent and rate of drug release remained same and only the amount or extent of drug release was increased.

All the developed tablet formulations exhibited a biphasic release profile as an initial fast drug release phase (burst effect) was followed by a sustained, gradually increasing drug release phase after 1-2 h extending up to 15-24 depending upon proportion of matrix forming polymer used in the tablet formulations.

By fitting the release data into the Korsmeyer-Peppas equation, the values of n for all aceclofenac tablet formulations was ranged from 0.641 to 0.962, indicating drug release could have occurred by a diffusion process . High values of correlation coefficient ranging from 0.9993 to 0.9836 indicate goodness of fit of dissolution data to the power law equation for HPMC, XG and GG containing tablets.
The stability studies were carried out on optimized tablet batch formulation AHG20 at 400C/75%RH for 30 days to assess their long term stability. After storage 400C/75%RH for 30 days the formulation were observed for physical change, drug content and subjected to in vitro drug release studies. No change in physical appearance, physical properties and in drug content was observed .When the dissolution study was conducted there was no significant difference in the percent of aceclofenac released from formulation AHG20 when compared with that drug released from the same formulation before storage .This insignificant change in the physical appearance, physical parameters and drug content and in dissolution pattern of AHG20 formulation after storage for 30 days indicates that the developed formulation could provide a better shelf life.

CONCLUSION:

The additives which are used in the tablets were cost effective and are very easily available. Most of the excipients used in formulation are water swellable and hence may have a better patient acceptability. The present research work of preparing a oral controlled release matrix tablet containing aceclofenac was successful in terms of reducing manufacturing difficulties, cost and providing a better patient compliance with effective medication. It has been observed from the above study that excipients like HPMC, xanthan gum, guar gum and microcrystalline cellulose were ideal excipients and effective for formulating controlled release matrix tablets. As these excipients are easily available, inexpensive and compatible. Controlled release matrix tablets provide several advantages especially improves bioavailability, reduces drug waste and improves patient compliance. The batch AHG20 was considered to be the best among all other batches since it exhibited a good dissolution profile, total controlled release matrix time, uniformity of drug content, and further good stability.

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