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Design and evaluation of multi particulate system of extended release indomethacin capsules USP

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ABSTRACT

In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities. There are so many oral delivery systems in that one of the advance techniques is Pellatization. Indomethacin extended release capsules prepared by pellatization method that the indometahcin is coated on inert sugar spheres by using povidoneK-30 as a binder solutions and Hydroxypropylmethylcellose, Ethyl cellose coating agents used for extended release action. The prepared capsules were evaluated for content uniformity weight variation, in-vitro disintegration time, assay, and in-vitro drug release study. All the formulation exhibited assay, content uniformity with in the range given in USP. Dissolution studies revealed that formulations containing Cross povidone-k 30 2.31gm coating agent Hydroxypropylmethylcellose, 0.312gm of ethyl cellose 0.216gm Showed 100% of drug release, at the 12th hour. The concentration of coating agents Hydroxtpropylmethycellose and Ethyl cellose had an effect on in-vitro drug release had the same drug release profile when compare with US dissolution parameters, and reference drug release. Thus, the capsules apart from fulfilling all official and other specifications and exhibited higher rate of drug release.

Key words: Indomethacin, Hydroxy propyl methyl cellose, Ethyl cellose Povidone-30

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INTRODUCTION

The treatment of acute diseases or chronic illness has been achieved by delivery of drugs to the patients for many years. These drug delivery systems include tablets, injectables, suspensions, creams, ointments, liquids and aerosols. Today these conventional drug delivery systems are widely used. The term drug delivery can be defined as techniques that are used to get the therapeutic agents inside the human body. Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic window. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels in the body [1].

Controlled drug delivery

The delivery of drug at a rate or at a location determined by needs of body or disease state over a specified period of time.

The oral controlled release systems are classified as follows:

A) Continuous release systems
B) Extended release systems
C) Time release systems

The release system is formulated to dissolve solely and release a drug over time. The advantages of Controlled release tablets capsules are that they can often less frequently than instate release formulations [2,3].

EXTENDED RELEASE DRUG DELIVERY SYSTEM

Extended release system was introduced in the pharmaceutical market in the early 1950S by Smith Kline and French made an orally administrated formulation of dextroamphetamine sulphate by incorporating the drug in pellets coated with wax. Conventional drug products like tablets and capsules are formulated to release the active drug immediately to obtain rapid and complete systemic absorption of the drug. The conventional dosage form maintains the constant plasma drug concentration for the long period of time by administering in a particular dose and at particular frequency. The terms sustained release, time release, prolong release or extended release are used to identify drug delivery systems that are designed to achieve a prolonged therapeutic blood or tissue levels of the drug by continues release of the extended period of time after administration of a single dose. Extended release dosage forms release drug slowly ,so that plasma concentrations are maintained at a therapeutic level prolonged period of time (usually12 hrs) Extended drug action at a pre determined rate by maintaining a relative constant ,effect drug level in the body

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with concomitant minimization of undesirable side effects that associated with a saw tooth kinetic pattern of conventional release [4,5].

REASONS FOR DEVELOPING EXTENDED RELEASE DRUG DELIVERY SYSTEM

Immediate release of the active ingredient with resulting fast absorption rate may not always be desirable. If the drug has narrow therapeutic index, fast and complete absorption may result in plasma concentration that corresponds to toxic levels [6].

The aim and objectives of the present study was to develop a pharmaceutically equivalent, stable, cost effective and quality improved formulation of Indomethacin pellets to present it in the form of capsules (Extended release capsules) and these were compared with that of the marketed dosage form. To achieve this goal various prototype formulation trails were taken and evaluated with respect to the various quality control such as dissolution, assay, acid resistance and moisture content. The formula was finalized by comparing the in vitro dissolution profile with that of the marketed product.

MATERIALS AND METHODS

Table: 1 [7]

S.No.	Name of the ingredients	Category
1.	Sugar spheres	Inert cores
2.	Povidone K-30 USP	Binder
3	Isopropyl alcohol USP	solvent
4.	Talc USP	Anti charging agent
5	Hydroxypropylmethyl cellose(6cps) USP	Coating agent
6	Ethyl cellose USP	Coating agent

PREPARATION OF INDOMETHACIN PELLETS [8]

Drug coating

Equal quantities of Indomethacin and other excipients are weighed

Indomethacin suspension preparation

Dissolve povidone K-90 in isopropyl alcohol with continuous stirring till to get clear solution. Add Indomethacin and Mannito to the above solution. Continue stirring till to get clear solution.

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Coating of indomethacin

Load the sugar spheres (30-35mesh) into Fluidized bed coater 3 kg using following parameters. After completion of indomethacin suspension coating, contained the coating using the isopropyl alcohol to eliminate the loss of active substance from tube and the spray nozzles. Dried the drug coating pellets at the temperature of 28-32^{0}C till to get LOD less than 1%.

Sieving

Shift the pellets from sieve #18 mesh, collected the #18 mesh passing. Shifting the #18 mesh passing through #25 mesh retained pellets and labeled as 18/25 fraction pellets.

Blending

Shift talc through mesh #40 .load the granules to octonal blender and added the materials and blend for 5 min.

Preparation of sub coating solution

Dissolve the Hydroxy propyl methylcellose Ethyl cellose in water stir it for 5min to form uniform solution Spray the coating solution by using Fluidized bed coater Maintain the required conditions in coater Collect #25 passed #20 retained fines Totally 6 Formulation trails were done using the same procedure.

Filling

Filling of the pellets into capsules by hand operated capsule filling machine**.**

EVALUATION OF EXTENDED RELEASE CAPSULES [9-26]

PHYSICAL EVALUATIONS

Weight variation test

Individual weights of 20 capsules were taken and the average weight was calculated by using the following formula.

$$\text{Weight variation} = \frac{\text{(Weight of capsule-Average weight)}}{\text{Average weight of capsules}} \times 100$$

Weight variation should not be more than 7.5%. Results are tables in table no: 2

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Lock length

It was tested by using vernier calipers. Results are tables in table no: 2

Physical Evaluations

Table: 2

S no	parameter	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
1	Weight variation	Not with in limit	Not with in limit	Not with in limit	Not with in limit	Not with in limit	Not within the limit	with in the limit
2	Lock length	Not with in limit	Not with in limit	Not with in limit	Not with in limit	Not with in limit	Not With in the limit	With in the limit

CHEMICAL EVALUATIONS

Dissolution

For capsules place 900ml of dissolution medium n each vessel and allow the medium to equilibrate to a temperature of 37 ± 0.5 ºC .place one capsules in each of the basket and operate the apparatus at 75 rpm for specific time. With draw 10ml of the solution from each vessel and replace with equal volume of fresh dissolution medium at specific time intervals. Filter the solution through 0.45microns membrane filter and discard first few ml of the filtrate. The results are shown in table no: 3

Chemical Evaluations

Table: 3

S.no	Parameter	Trial1	Trial2	Trial 3	Trial4	Trial5	Tria6	Tria7
1	Assay%	Not with in limit	Not with in limit	Not with in limit	Not with in limit	Not with in limit	Not With in the limit	With in the limit
2	Dissolution	Not with in limit	Not with in limit	Not with in limit	Not with in limit	Not with in limit	Not With in the limit	With in the limit

Assay

Standard preparation

Accurately weighed and transfer about 50mg of indomethacin working standard into a 100ml volumetric flask. Add about 25ml of acetonitrile and sonicate to dissolve .Dilute to 0.5ml of the above solution with diluent and mix well.

Sample preparation

Weigh and mix the contents of not less than 20 capsules .accurately weighed and transfer a portion of the pellets equivalent to about 100mg of indomethacin into a 200ml

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volumetric flask add 80ml of diluent, and sonicate until the pellets are disappear with occasional shaking .add about 100ml of acetonitrile and mix. Centrifuge a portion of this solution. Diluent 5ml of the supernatant solution to 50ml with diluent and mix. Filter the solution through 0.45microns membrane filter. The results are shown in table no: 3

DISSOLUTION PROFILE OF TRAIL BATCHES

Time (Hrs)	TRAIL BATCHES %DRUG RELEASE							
	Reference	Trail-1	Trail-2	Trail-3	Trail-4	Trail-5	Trail-6	Trail-7
1	30	19	37	23	21	41	36	30
2	51	42	58	50	41	50	56	52
3	71	74	75	67	58	62	72	73
4	92	81	86	87	72	89	91	97

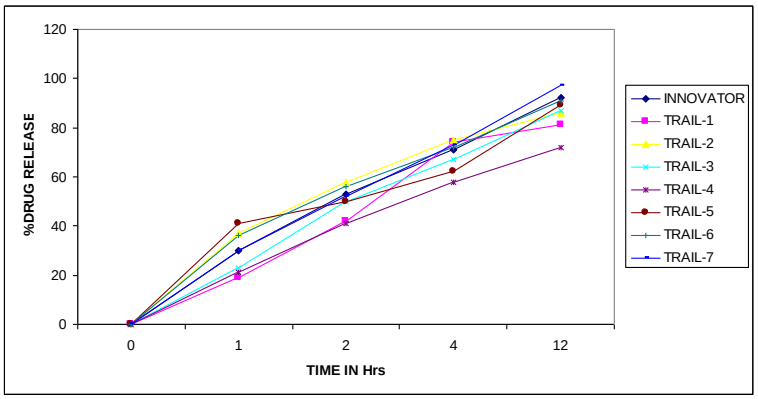
RESULTS AND DISCUSSION

Weight variation test, Lock length, Assay results are tabled in table no: 2, 3 dissolution graphs are presented in fig no: 1

STABILITY STUDIES

All stability study assay results are tabled in table no: 4. Dissolution studies results are tabled in table no: 5, 6, and 7

Fig. No:-1: %DRUG RELEASE PROFILE OF TRAIL BATCHES



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CONCLUSION

Trial 7 (optimized batch) preparations will have more %drug release than the innovator product. The other parameters (assay weight variation, capsule length) are also with in the USP recommended range.

Table: 4: STABILITY STUDIES

S.No	Parameter	Accelerated Stability studies of formulation stored at different conditions		
		25ºC ± 2 ºC/ 60% RH ± 5%	30ºC ± 2 ºC/ 60% RH ± 5%	40ºC ± 2 ºC/ 60% RH ± 5% RH
1	Assay	99%	99%	99%

Table no-5: Dissolution profile of stability batch of Trial-7

Time (hr)	Long term Storage condition(12 months)		
	Controlled	Room temperature	25°C±2ºC/60% RH ± 5% RH
0	0.00	0.00	0.00
1	30	30	30
2	51	52.	52
4	71	73	73
12	92	97	97

Table no-6:Dissolution profile of stability batch of Trial-7

Time (hr)	Intermediate Storage condition(6months)		
	Controlled	Room temperature	30°C±2ºC/60% RH ± 5% RH
0	0.00	0	0
1	30	30	30
2	51	52	52
4	71	71	71
12	92	97	97

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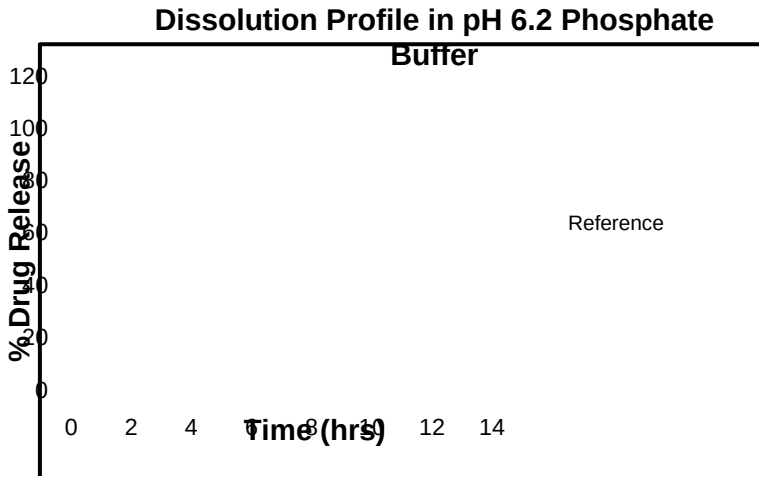
Table no: 7: Dissolution profile of stability batch of Trial-7

Time (hr)	Accelerated Storage condition(6 months)		
	Controlled	Room temperature	40°±2ºC/75% RH ± 5% RH
0	0.00	0	0
1	30	30	30
2	51	52	52
4	71	71	71
12	92	97	97

Fig. No: 2: Dissolution profile of stability batch of Trial-7



When significant changes not occurs at any time during 12 and 6 months testing at the accelerated storage condition, additional testing at the intermediate storage condition conducted and evaluated tests for assay, and dissolution studies.

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