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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *of inventorship (Rule 4.17(iv)) for US only*

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(54) Title: PHARMACEUTICAL COMPOSITIONS AND PROCESS OF PRODUCTION THEREOF

(57) Abstract: A novel extended release oral solid dosage formulation of metoprolol succinate is provided which includes an extended release polymer base retardant coating and a process of production thereof. In the present invention metoprolol succinate tablets comprising of strengths varying from 12.5 to 200mg are prepared via a wet granulation method and the formulation for release of metoprolol for upto 24 hours is provided.

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PHARMACEUTICAL COMPOSITIONS AND PROCESS OF PRODUCTION THEREOF

Related Applications:

This application claims priority from India National application serial No. 151/MUM/2003, filed 05 February 03.

Field of the Invention

The invention relates to the field of medicine and pharmacology. More specifically, the invention relates to an extended release oral dosage pharmaceutical composition comprising metoprolol or a pharmaceutically acceptable succinate salt thereof provided with an extended release polymer base retardant coating, and to a process for its production.

Description of Related Art

Metoprolol succinate is a beta-selective (cardioselective) adrenoreceptor blocking agent, for oral administration, available as extended release tablets to treat the heart condition angina. The drug reduces the oxygen demand to the heart, slowing the heart rate, reducing cardiac output when at rest and on exercise and reduces systolic blood pressure among other things. There are many controlled and sustained release

metoprolol formulations already known, which usually comprise controlled release pellets, wherein each pellet acts as a separate drug delivery unit. But in order to obtain a desirable release of a drug, a considerable amount of experimentation needs to be performed. So, in accordance with the present investigation, an extended release pharmaceutical formulation has been devised which releases the drug for up to 24 hours in a suitably controlled manner.

U.S. Patent 4792452 to Howard et al., describes a controlled release pharmaceutical formulation which releases the drug at a controlled rate regardless of the pH of the environment. Its formulation includes up to about 45% by weight of a pH dependent polymer, which is a salt of alginic acid in addition to a pH independent hydrocarbon gelling agent, such as hydroxypropylmethyl cellulose.

EP 0293347 to Henry A.C. and Christina E.E. describes metoprolol succinate as a new therapeutically active compound, and pharmaceutical preparations comprising it. This invention discusses a new oral, therapeutically active compound, which is soluble in the pH range 1 to 8, which therefore can be released in the gastrointestinal tract below the upper part of the small intestine. The sustained release excipient is prepared by dry blending the requisite amounts of xanthan gum, dextrose and calcium sulfate.

U.S. Patent 4871549 to Yoshio U. et al., describes a time controlled explosion system comprising metoprolol, a swelling agent such as a low substituted

hydroxypropylcellulose, sodium starch glycolate or carboxymethylcellulose sodium, coated with a water-insoluble coating material so that drug release is caused by the explosion of the membrane after a definite time period.

U.S. Patent 4957745 to Jonsson U.E. et al describes the pharmaceutical preparation of a controlled release preparation containing a number of beads comprising metoprolol salts, their production and use in cardiovascular disorders.

U.S. Patent 4927640 to Dahlinder L-ED et al also describes controlled release beads having a glass or silicon dioxide core. Metoprolol succinate was sprayed onto the cores of silicon dioxide, glass and sodium chloride from a solution of ethanol 95% and methylene chloride. Then the coated beads were filled into hard gelatin capsules.

U.S. Patent 5081154 to Henry A.C. and Christina E.E. which is a continuation of EP 0293346 also relates to metoprolol succinate wherein an oral pharmaceutical composition comprising a core containing a therapeutically active compound is disclosed. The core has been coated with a layer comprising an anionic polymer and a water insoluble polymer selected from the group of quaternary ammonium substituted acrylic polymers. The investigators suggest that in order to achieve a steady blood plasma level of the therapeutically active compound, a split dose unit of the therapeutically active compound provided with a coating according to the present

invention can be administered together with some particles/granules which are not coated.

U.S. Patent 5399358 to Stanoforth George N and Baichwal Anand R is directed to sustained release formulations which provide a 24 hour release of metoprolol using a combination of xanthan gum with locust bean gum as the preferred gum combination.

EP Application 110542 by McCall Troy W and Baichwal Anand R describes once-a-day oral dosage form of metoprolol to be released over a period of 24 hours in the gastrointestinal tract. The sustained release matrix comprises heterosaccharide derivatives of xanthan gum.

A number of patents in the prior art deal with sustained or controlled release formulations of metoprolol. These include water insoluble glass, silicon dioxide or plastic resin beads, which are sprayed with metoprolol salt and then coated with controlled release polymeric membrane. Another sustained release excipient commonly used is a heteropolysaccharide e.g., xanthan gum or a gum combination of xanthan and locust bean gum for delaying the drug release. In other cases there is the use of a heteropolysaccharide gum along with a homopolysaccharide gum, which can cross-link with the heteropolysaccharide gum in the gastro-intestinal fluid. Thus there is a need for a simple and economical process of formulation of metoprolol succinate extended release drug which the present invention attempts to address with the use of wet

granulation method with carbomers and a water insoluble hydrophobic polymer retarding coating of ethyl cellulose to provide up to 24 hours of extended release of metoprolol.

Summary of the Invention

It is an object of the invention to provide an improved pharmaceutical composition, in particular for the treatment of angina. It is a further object of the invention to overcome or ameliorate one of more of the problems associated with the prior art pharmaceutical preparations. It is also an object of the present invention to provide a sustained release oral dosage pharmaceutical composition comprising metoprolol or a succinate salt thereof. It is further an object of the invention to provided a process for the production of such a pharmaceutical composition.

According to the present invention, there is provided a pharmaceutical composition comprising a matrix material having metoprolol, or a pharmaceutically acceptable salt thereof, dispersed therein, the dispersion of the metoprolol or pharmaceutically acceptable salt thereof within the matrix material being effective to delay the release profile on administration of the pharmaceutical composition, the tablet being provided with a substantially water-insoluble polymeric coating effective further to delay the release profile on administration of the pharmaceutical composition.

Detailed Description

Preferably, pharmaceutically acceptable salt is a succinate. The matrix material may be capable of forming a swelling gel when in contact with water and may comprise a

cellulosic polymer and a carbomer. The cellulosic polymer is preferably hydroxypropyl methyl cellulose.

The polymeric coating may comprises cellulose derivatives without protolysable groups, for example ethyl cellulose.

The metoprolol, or pharmaceutically acceptable salt thereof, is preferably provided in the form of a granulated active ingredient. It may be present in an amount of from 12.5mg to 200mg in the composition, for example in an amount of 12.5mg, 25mg, 50mg, 100mg or 200mg in the composition.

The pharmaceutical composition according to the invention may further comprise a binder, for example a povidone.

The hardness of the tablet may vary from 35 Nortons to 160 Nortons for tablets of different strengths.

One preferred pharmaceutical composition according to the invention comprises:

metoprolol succinate	27 to 30%
microcrystalline cellulose	17 to 30%
carbomer	1 to 6%
hydroxypropyl methyl cellulose (K100M)	14 to 56%
hydroxypropyl methyl cellulose (K4M)	4 to 10%
povidone	8 to 12%
magnesium stearate	1 to 1.5%
isopropyl alcohol	q.s.

and the coating comprises:

opadry 04-C-7000 A (colorcon)	4 to 5%
ethyl Cellulose	1 to 2%
isopropyl alcohol	q.s.
methylene chloride	q.s.

Preferably, the weight ratio of metoprolol, or pharmaceutically active salt thereof, to carbomer is in the range of 10:1 to 1:12.

Also provided in accordance with the invention is a process for the production of a pharmaceutical composition according to the invention, comprising blending

metoprolol, or a pharmaceutically acceptable salt thereof, with a matrix material, granulating the blended mixture and compressing to form a tablet, and spray coating the tablet with a polymeric coating.

At least one carbomer is preferably introduced into the composition during the blending and granulation steps.

Preferably, the tablet is prepared by a wet granulation process, preferably a non-aqueous process, for example a process using a hydroalcoholic wetting material

Accordingly, the invention provides a process for preparing a pharmaceutical composition comprising:

a) introduction of metoprolol succinate, carbomer and hydroxy polymethyl cellulose by blending, milling and sieving prior to granulation
b) introduction of a solution of polymer in non-aqueous / hydroalcoholic solvent during granulation of the blended material as in (a)
c) spray coating of the compressed tablets as in (c), with a water-insoluble polymeric membrane containing derivatives of cellulose without protolyasable groups
d) thereby incorporating the tablet and the coating into a matrix forming a swelling gel in contact with water.

This, in accordance with the present invention, there is provided a process for producing pharmaceutically extended-release preparations of metoprolol succinate. The object of this invention is to obtain a solid preparation with high bioavailability of the drug in combination with an extended absorption in the gastrointestinal tract thus achieving an even effect of up to 24 hours after one (or twice in case of a lower dosage such as 12.5mg) daily administration.

The present invention further provides a process for producing oral solid extended release pharmaceutical formulations, which releases metoprolol succinate over a time period of up to 24 hours.

In the embodiments of the invention, the carbomer is included in an amount from about 4.54% to about 11.5%, by weight of the final product. The drug to carbomer ratio may be, from about 10:1 to about 1:12 for example. Preferably, the drug to carbomer ratio is from about 10:1.25 to about 1:12 by weight of formulation.

The preparation of the said tablet is by compression and mixing of polymers. The carbomers are used in both granulation as well as mixing stages.

By "extended release" it is meant for purposes of the present invention that the therapeutically active medicament is released from the formulation at an extended rate such that therapeutically beneficial blood levels (but below toxic levels) of the

medicament are maintained over an extended period of time, e.g., providing a 24 hour dosage form.

The term "environment" is meant for purposes of the present invention to encompass a mammalian body, an organ of such a body or area of such a body, for example, the gastro-intestinal area. Such an environment can be tested by means of in-vitro dissolution testing, as is standard practice for testing of therapeutically active substances prior to use in mammalian bodies.

By using a careful choice of fillers and binders as well as gel forming materials the preparation may be manufactured into a commercially acceptable form, e.g. a tablet that shows unexpectedly good bioavailability of both active compounds as well as a prolonged duration of action.

Specific embodiments of the present invention will now be described by way of example only with reference to and as illustrated in the following examples.

EXAMPLE 1

Wet Granulation Method for Compression

The active ingredient, MCC, carbopol and HPMC were blended together, and then the blend milled through a screen with appropriately size mesh. The blended material was

then granulated with a solution of polymer in non-aqueous/ hydroalcoholic solvent. The granules were then dried at a suitable temperature and screened through a mesh of appropriate size. The blend was lubricated with a soluble or insoluble lubricant. The tablets were then formed by compression.

The pharmaceutical composition of the tablets containing 100mg metoprolol succinate without carbomer had the following composition:

TABLE 1

Ingredients	**Parts by weight of tablet**
Metoprolol succinate	27.14 %
Micro Crystalline Cellulose	25.71 %
Hydroxy propyl methly cellulose (K4M)	4.28 %
Hydroxy propyl methly cellulose (K100M)	14.29 %
Povidone	8.57 %
Isopropyl alcohol	qs
Hydroxy propyl methly cellulose (K4M)	4.28 %
Hydroxy propyl methly cellulose (K100M)	14.29 %
Magnesium stearate	1.43

Tablets containing 12.5mg, 25 mg, 50 mg, and 200 mg metoprolol succinate were similarly prepared.

EXAMPLE 2

The coating solution to be applied to the tablets had the following composition:

TABLE 2

Ingredients	**Parts by weight of tablet**
Hydroxy propyl methyl cellulose 15cps	5 %
Poly ethyene glycol 400	0.5 %
Talc	0.7 %
Titanium dioxide	3.8 %
Isopropyl alcohol	qs
Methylene chloride	qs

There was a 3% weight gain by coating.

EXAMPLE 3

Tablets containing 100 mg dose of metoprolol with carbomer were produced and had the following composition:

TABLE 3

Ingredients	Parts by weight of tablet
Metoprolol succinate	28.35 %
Micro Crystalline Cellulose	17.91 %
Carbomer	1.49 %
Hydroxy propyl methyl cellulose (K100M)	28.35 %
Povidone	10.45 %
Iso propyl alcohol	qs
Carbomer	4.47 %
Hydroxy propyl methyl cellulose (K100M)	28.35 %
Magnesium stearate	1.49 %

Tablets containing 12.5mg, 25 mg, 50 mg, and 200 mg were similarly prepared.

EXAMPLE 4

Retarding Coating Solution

A retarding coating solution with the following composition was used to further coat the tablets from Examples 1 and 3.

TABLE 4

Ingredients	**Parts by weight of Tablet**
Opadry OY-C-7000A (M/S coloreon)	4.5 %
Ethyl cellulose	1.0 %
Iso propyl alcohol	qs
Methylene chloride	qs

In this case, a 6-7% weight gain after coating was noted.

EXAMPLE 5

Dissolution tests were then carried out for the tablets produced in Examples 1-4. The dissolution tests were conducted in an automated USP dissolution apparatus (Paddle type II, pH 6.8 buffer, 50 rpm). The results are given in Table 5 & 6.

TABLE 5: Carbomers with matrix control only

Time in hours	Example 1(core)	Example 2 (coated)	USP Limits
1	15.19%	13.90%	NMT 25%
4	35.32%	34.46%	20-40%
8	52.43%	51.70%	40-60%
20	101.92%	103.19%	NLT 80%

TABLE 6: Polymers with retardant coating.

Time in hours	Example 3 (core)	Example 4 (coated)	USP Limits
1	21.28%	17.51%	NMT 25%
4	37.45%	39.24%	20-40%
8	59.05%	58.88%	40-60%
20	96.38%	103.11%	NLT 80%

From the dissolution results in Table 5 & 6, it can be inferred that formulations made with carbomer had slower drug release rates compared to formulations made without carbomer. Furthermore, it was also noticed that formulations with the retarding coating had slower drug release rates when compared to those not coated with retarding coating.

Similar dissolution results were seen with 12.5, 25, 50 and 200mg formulations.

References

Beta-blockers in chronic heart failure: considerations for selecting an agent. Mayo Clin Proc 2002 Nov;77(11):1199-206.

Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure. J Am Coll Cardiol 2002 Aug 7;40(3):491-8.

Successful blood pressure control in the African American Study of Kidney Disease and Hypertension. Arch Intern Med 2002 Jul 22;162(14):1636-43.

Metoprolol CR/XL in female patients with heart failure: analysis of the experience in Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure. Circulation 2002 Apr 2;105(13):1585-91.

Tolerability of beta-blocker initiation and titration in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure.Circulation 2002 Mar 12;105(10):1182-8.

Effects of metoprolol CR/XL on mortality and hospitalizations in patients with heart failure and history of hypertension.J Card Fail 2002 Feb;8(1):8-14.

Effect of controlled release/extended release metoprolol on carotid intima-media thickness in patients with hypercholesterolemia: a 3-year randomized study. Stroke 2002 Feb;33(2):572-7.

Longitudinal myocardial contraction improves early during titration with metoprolol CR/XL in patients with heart failure. Heart 2002 Jan;87(1):23-8.

CLAIMS

1. A pharmaceutical composition comprising a matrix material having metoprolol, or a pharmaceutically acceptable salt thereof, dispersed therein, the dispersion of the metoprolol or pharmaceutically acceptable salt thereof within the matrix material being effective to delay the release profile on administration of the pharmaceutical composition, the tablet being provided with a substantially water-insoluble polymeric coating effective further to delay the release profile on administration of the pharmaceutical composition.
2. A pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable salt is a succinate.
3. A pharmaceutical composition according to claim 1 or claim 2, wherein the matrix material is capable of forming a swelling gel when in contact with water.
4. A pharmaceutical composition according to any one of claims 1 to 3, wherein the matrix material comprises a cellulosic polymer and a carbomer.
5. A pharmaceutical composition according to claim 4, wherein the cellulosic polymer is hydroxypropyl methyl cellulose.
6. A pharmaceutical composition according to any one of claims 1 to 5, wherein the polymeric coating comprises cellulose derivatives without protolysable groups.

7. A pharmaceutical composition according to claim 6, wherein the polymeric coating comprises ethyl cellulose.

8. A pharmaceutical composition according to any one of claims 1 to 7, wherein the metoprolol, or pharmaceutically acceptable salt thereof is provided in the form of a granulated active ingredient.

9. A pharmaceutical composition according to any one of claims 1 to 8, further comprising a binder.

10. A pharmaceutical composition accoridng to claim 9, wherein the binder is a povidone.

11. A pharmaceutical composition according to any one of claims 1 to 10, wherein the metoprolol, or pharmaceutically acceptable salt thereof is present in an amount of from 12.5mg to 200mg in the composition.

12. A pharmaceutical composition according to claim 11, wherein the metoprolol, or pharmaceutically acceptable salt thereof is present in an amount of 12.5mg, 25mg, 50mg, 100mg or 200mg in the composition.

13. A pharmaceutical composition according to any one of claims 1 to 12, wherein the hardness of the tablet varies from 35 Nortons to 160 Nortons for tablets of different strengths.

14. A pharmaceutical composition according to any one of claims 1 to 13, comprising:

metoprolol succinate	27 to 30%
microcrystalline cellulose	17 to 30%

carbomer	1 to 6%
hydroxypropyl methyl cellulose (K100M)	14 to 56%
hydroxypropyl methyl cellulose (K4M)	4 to 10%
povidone	8 to 12%
magnesium stearate	1 to 1.5%
isopropyl alcohol	q.s.
and wherein the coating comprises:	
opadry 04-C-7000 A (colorcon)	4 to 5%
ethyl Cellulose	1 to 2%
isopropyl alcohol	q.s.
methylene chloride	q.s.

15. A pharmaceutical composition according to any one of claims 1 to 14, wherein the weight ratio of metoprolol, or pharmaceutically active salt thereof, to carbomer is in the range of 10:1 to 1:12.

16. A process for the production of a pharmaceutical composition according to any one of claims 1 to 15, comprising blending metoprolol, or a pharmaceutically acceptable salt thereof, with a matrix material, granulating the blended mixture and compressing to form a tablet, and spray coating the tablet with a polymeric coating.

17. A process according to claim 16, wherein at least one carbomer is introduced into the composition during the blending and granulation steps.

18. A process according to claim 16 or claim 17, wherein the tablet is prepared by a wet granulation process.

19. A process according to claim 18, which is non-aqueous.

20. A process according to claim 19, which is hydroalcoholic.

21. A process according to any one of claims 16 to 20 comprising:

a) introduction of metoprolol succinate, carbomer and hydroxy polymethyl cellulose by blending, milling and sieving prior to granulation

b) introduction of a solution of polymer in non-aqueous / hydroalcoholic solvent during granulation of the blended material as in 1(a)

c) spray coating of the compressed tablets as in 1(c), with a water-insoluble polymeric membrane containing derivatives of cellulose without protolyasable groups

d) thereby incorporating the tablet and the coating into a matrix forming a swelling gel in contact with water.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00312-0

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: A61K 31/135, 9/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAS, Medline

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0148811 A1 (LEJUS MEDICAL AKTIEBOLAG) 17 July 1985 (17.07.85) *claims 1-6.*	16, 18-21
X	WO 02/058677 A1 (ASTRAZENECA AB) 1 August 2002 (01.08.02) *claims 1-9.*	16, 18-21
Y	EP 0293347 A1 (LEJUS MEDICAL AKTIEBOLAG) 30 November 1988 (30.11.88) *claims.*	16, 18-21
Y	EP 0210540 A1 (FUJISAWA PHARMACEUTICAL CO., LTD.) 4 February 1987 (04.02.87) *claims.*	16, 18-21
A	EP 0237345 A2 (WASHINGTON UNIVERSITY TECHNOLOGY ASSOCIATES, INC.) 16 September 1987 (16.09.87) *abstract, claims 1-7.*	16-21

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed
„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 February 2004 (12.02.2004)	10 March 2004 (10.03.2004)
Name and mailing adress of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. 1/53424/535	Authorized officer MOSSER R. Telephone No. 1/53424/437

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00312-0

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-3
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

As claims 1-3 are function-orientated the search has been carried out on basis of disclosure given by claim 4.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN 03/00312-0

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
EP A 148811		DE	T	3586206T	1992-12-24
		DE	D	3586206D	1992-07-16
		DE	D	3572767D	1989-10-12
		AT	T	77077T	1992-06-15
		AT	T	46080T	1989-09-15
		LV	A	5814	1997-04-20
EP A 210540		CA	C	1282698	1991-04-09
		IE	L	861884L	1987-01-19
		DE	D	3682135D	1991-11-28
		AT	T	68696T	1991-11-15
		DK	A	344586	1987-01-20
		US	A	4871549	1989-10-03
EP A 237345		CA	C	1321692	1993-08-31
		PL	A	264591	1988-04-28
		CN	A	87101837	1987-12-02
		DE	D	3770843D	1991-07-25
		BR	A	8707635	1989-03-14
		ZA	A	8701163	1987-09-30
EP A 293347		DE	T	3586206T	1992-12-24
		DE	D	3586206D	1992-07-16
		DE	D	3572767D	1989-10-12
		AT	T	77077T	1992-06-15
		AT	T	46080T	1989-09-15
		LV	A	5814	1997-04-20
WO A 58677		none			