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Research Article

DESIGN, DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE DRUG COMBINATION

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ABSTRACT

Therapeutic success of any therapy depends on the patient's compliance to ward the therapy. Tablets are the most popular dosage form because of its unique properties such as ease of administration, low cost and non-invasive therapy etc.The present study aims to develop and evaluate to provide polytherapy through a single tablet in which combination of Atorvastatin (antihyperlipidemic) and Gliclazide (antidiabetic) were used. Since Atorvastatin has $t_{1/2}$ is near about 5 hours so its release was retarded. H.P.M.C. was used as a retardant material. Two grades of H.P.M.C. i.e. - H.P.M.C. 4000cps and H.P.M.C. 100cps were used.The tablets were prepared by wet granulation method and were compressed with punches of diameter 12.4mm. Granules property and tablets characteristics were evaluated following standard procedure. In vitro dissolution studies were conducted in USPXXIII apparatus at 50 rpm up to 8 hours. First two hour of dissolution study was carried out using medium 0.1N HCI and from 3rd to 8th hour the study was done using medium phosphate buffer of pH 6.8. For Atorvastatin only two hours of dissolution study was performed and its release was found to be 97.6%. For Gliclazide dissolution study was performed up to complete 8 hour and its release was found to be 89.314% and release rate was found to be nearly similar to marketed product.

Key words: Gliclazide, Atorvastatin, polytherapy, H.P.M.C.

INTRODUCTION

The present study aims to develop and evaluate to provide polytherapy through a single tablet in which combination of Atorvastatin (antihyperlipidemic) and Gliclazide (antidiabetic) were used. Gliclazide is used in treatment of diabetes mellitus, and it is classified under oral biguanides. Atorvastatin is used for the treatment of hyperlipidemic disorder . Both drugs are combined to treat the diabetic obese patients.Two grades of H.P.M.C. i.e. - H.P.M.C. 4000cps and H.P.M.C. 100cps were used.The tablets were prepared by wet granulation method and were compressed with punches of diameter 12.4mm. No literature survey has been found regarding this work. atorvastatin calcium is used which is from biocon India ltd. First two hour of dissolution study was carried out using medium 0.1N HCI and from 3rd to 8th hour the study was done using medium phosphate buffer of pH 6.8. For Atorvastatin only two hours of dissolution study was performed and its release was found to be 97.6%. For Gliclazide dissolution study was performed up to complete 8 hour and its release was found to be 89.314% and release rate was found to be nearly similar to marketed product.

MATERIALS AND METHODS

Protype Formulation

Formula F6

To take a batch of Atorvastatin Calcium with Gliclazide having 50% of HPMC 4000 cps & 50% of HPMC 100 cps where total polymer conc. was 20 % to that of Gliclazide granules weight.

Dissolution medium:

(For Gliclazide)
First 2 hour in 0.1 n hcl.
From 3rd to 8th hour in 6.8 phosphate buffer
(For Atorvastatin)
Only two hour study in 0.1 n hcl
Limits to pass the dissolution test:
(For Gliclazide)
In between 4 – 6 hour the release of drug should be at least 50%.
(For Atorvastatin)
Within 30 minutes, the release of atorvastatin should not be less then 75%.

RESULT AND DISCUSSION

The study was undertaken with an aim to formulate combination of anti diabetic and antihyperlipidemia drugs. The literature review showed that Atorvastatin Calcium is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methyl glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol (Antihyperlipoproteinemix agent). Due to this reason it is used mainly in the treatment of diabetic dyslipidemia.Gliclazide is a second-generation sulphonyl urea an anti hyperglycemic agent that improves glucose tolerance in patients with type 2 diabetics. A sulphonylurea is a suitable alternative where people are not overweight.In present work an attempt has been made to formulate tablet containing immediate release Atorvastatin and sustained release Gliclazide using retardant namely hydroxypropyl methylcellulose. Two different grade of hydroxypropyl methylcellulose in different concentrations were used.In the preformulation study, compatibility evaluation was performed which implies that drugs, excipients and polymers are compatible with each other.The formulation of tablets was done by using wet granulation technique which was found acceptable.All the formulations were subjected to various evaluation studies. Results of the evaluation of granules and evaluation of tablet dimensions, hardness, friability, weight variation, content uniformity of active ingredient, in-vitro dissolution study, and comparison with marketed product. The results of evaluation studies can be summarized as follows: Results of evaluation of granules exhibited good flowability and compressibility.Uniformity in tablet dimensions implies that die fill was uniform and compression force was constant.Hardness values reveals that tables are having good mechanical strength and handling characteristics.Friability values dictate good compactness of the formulations.The weight variation of all formulated tablets were satisfactory, attributed by the acceptable flow properties of granules.

Content uniformity of active ingredient of all the formulations are within acceptable limit and ensures dosage uniformity.The promising formulations F6 obtained in evaluation studies were compared with marketed formulation. The evaluation parameters tested and compared, were drug content uniformity and in-vitro dissolution profile. The values obtained are recorded in Table No. 2. Mean value of drug content uniformity observed was 98.47 ± 0.578 for Gliclazide (Glizide MR) and 99.23 ± 0.580 for Atorvastatin (Lipifol). The marketed product (Glizide MR) gave 94.018 % of drug release in 8 hours of dissolution study and Atorvastatin (lipifol) showed 99.69 % release in 2 hours of dissolution study. The above study has shown that the in-vitro dissolution profile of formulation F6 was found to be comparable with that of marketed product, which was justified by the F2 value. F2 value obtained for Atorvastatin and Gliclazide was 58.03% and 53.58% respectively.Promising formulations was compared with marketed formulation, which shows that formulation exhibits drug release pattern, it was similar with marketed formulation.In vitro dissolution tests were performed and F2 values were calculated for optimized batch (F6). Dissolution profile matched with innovator products and F2 values were satisfactory.

Table 1: Formulation

Sr.No	Ingredients	Mg/ Tab	Qty / Batch (gms.)	Sr. No	Ingredients	Mg/Tab	Qty / Batch (gms.)
1.	Atorvastatin Calcium	10.800	10.800	1	Gliclazide	30	30
2.	Microcrystalline Cellulose PH101	59.000	59.000	2	H.P.M.C. 4000 cps	30	30
3.	Calcium Carbonate IP (Heavy)	34.50	34.500	3	H.P.M.C. 100cps	30	30
4.	Lactose Monohydrate	34.333	34.333	4	Microcrystalline Cellulose PH101	203.74	203.74
5.	Cross Caramellose Sodium BP	8.000	8.000	5	Hydroxy Propyl Cellulose 75 cps	6.261	6.261
6.	Hydroxy Propyl Cellulose 75 cps	3.140	3.140		Total LUBRICATION	300.00	300.00
7.	Polysorbate 80	0.650	0.650	1.	AEROSIL	3	3
8.	Sodium Ascorbate IP	0.0267	0.0267	2.	Talc IP	2.5	2.5
9.	Water purified IP	q.s.	q.s.	3.	Magnesium Stearate IP	2.5	2.5
Total		150.45	150.45		Total	8	8

Table 2: In-Vitro Dissolution Study For Formulation F6 (For Gliclazide)

Time In Hour	% Drug Release In 900 ml	% Drug Release In 10ml	Cumulative % drug released	Cumulative % drug retained
0.5	29.68	0.33	29.68	70.32
1.	35.9	0.39	36.62	63.38
2.	39.01	0.43	40.16	59.84
3.	12.43	0.138	52.59	47.41
4.	19.68	0.221	60.19	46.929
5.	26.82	0.210	67.551	40.449
6.	37.60	0.143	78.474	44.526
7.	43.53	0.140	84.544	40.456
8.	48.10	0.220	89.314	39.686

(For Atorvastatin)

Time In Hour	% Drug Release In 900 ml	% Drug Release In 10ml	Cumulative % drug released	Cumulative % drug retained
0.5	80.11	0.89	80.11	19.89
1.	88.9	0.98	90.77	9.23
1.05	94.68	97.6	97.6	2.4

Table 3: Evaluation of marketed sustained release tablets of gliclazide (glizide mr, b.no-2105009)
Test for Content of Active Ingredient

Parameter	I	II	III	Mean±S.D.
Content uniformity of active ingredient	97.81	98.89	98.71	98.47 ± 0.578

In-Vitro Dissolution Study

Time In Hour	% Drug Release In 900 ml	% Drug Release In 10ml	Cumulative % drug released	Cumulative % drug retained
0.5	10.5	0.117	10.5	89.5
1.	23.23	0.257	23.604	76.396
2.	23.80	0.323	24.497	75.503
3.	16.77	0.197	41.267	58.733
4.	25.03	0.277	50.00	50.00
5.	35.13	0.390	60.491	39.509
6.	44.00	0.500	69.861	30.139
7.	52.46	0.583	78.904	21.096
8.	66.83	0.744	94.018	5.982

Table 4: Evaluation of marketed tablets of atorvastatin(lipifol, b no-275601t)
Test for content of active ingredient

Parameter	I	II	III	Mean±S.D.
Content uniformity of active ingredient	99.67	98.51	99.11	99.23 ± 0.580

In-Vitro Dissolution Study

Time In Hour	% Drug Release In 900 ml	% Drug Release In 10ml	Cumulative % drug released	Cumulative % drug retained
0.5	85.54	0.95	85.54	14.46
1.	90.15	1.00	92.1	7.9
2.	96.67	1.07	99.69	0.31

REFERENCE

1. Li. V.H., "Influence of drug properties and routes of drug administration on the design of sustained and controlled release systems" chapter 1 in "Controlled drug delivery : fundamentals and applications" edited by Robinson J.R., Vincent Lee, 2nd edition, Marcel Dekker Inc., Volume 29, 1978: 5-36pp.
2. Longer M.A., Robinson J.R. "Sustained release drug delivery system" chapter 91 in "Remington's pharmaceutical sciences" 18th edition, Mack Publishing Company, 1990: 1675-1684pp.
3. Lordi N.G. "Sustained release dosage form" chapter 14 in "Theory and practice of Industrial Pharmacy" edited by Lachman et al., 3rd -edition, Varghese Publishing House, 1991: 430-431pp.
4. Welling P.G., Dobrinska M.R. "Dosing considerations and bioavailability assessment of controlled drug delivery systems" chapter 6 in "Controlled drug delivery : fundamentals and applications" edited by Robinson J.R., Vincent Lee, 2nd edition, Marcel Dekker Inc., Volume 29, 1978: 254-289pp.
5. Kumar S., Sharma S.M. 1991, "Controlled Release Dosage Forms" The Eastern Pharmacist, Sept.: 17-21pp.
6. Hui ho-wah, "Design and fabrication of oral controlled release drug delivery systems" chapter 9 in "Controlled drug delivery; fundamentals and applications", edited by Robinson J.R., Vincent Lee, 2nd edition, Marcel Dekker Inc., Volume 29, 1978: 391-420pp.
7. George M., Grass IV, Robinson J. "Sustained and controlled release drug delivery systems" chapter 6 in "Modern Pharmaceutics" edited by Banker G.S., Rhodes C.T., 2nd edition, Marcel Dekker, 1990: 639-658pp.
8. Gudsoorkar V.R., Rambhau D. 1993, "Sustained release of drugs". The Eastern Pharmacist, Nov.: 27-35pp.
9. Bechgaar H., Baggeson S., 1980, "Propoxyphene and norpropoxyphene : Influence of type of controlled release formulation on intra and intersubject variations", Journal of Pharmaceutical Sciences, 69 (11) : 1327-1330.
10. Kumar V., Damien B., Potdar A.R., 1992, "Designing of stability programme", The Eastern Pharmacist, Aug., 29-23.
11. Kaushal A. et al. 2001, "Regulatory requirements for oral controlled release drug delivery systems", Pharma Times, Volume 33, April, 14-17.
12. Martindale, Thirty-fourth edition, The Complete Drug Reference, Edited by-Sean C Sweetman, pharmaceutical press London, 2005, page no-332.
13. Physician's Desk Reference®, 56 edition 2002, published by Medical Economics Company, Inc at Montvale, page no-2639.
14. Patell MK, "Hydrxypropyl methylcellulose" in "Handbook of Pharmaceutical Excipients" published by American Pharmacist Association and the Royal Pharmaceutical Society of Great Britain 2006, 346-349pp.
15. LY Galichet, "Microcrystalline cellulose" in "Handbook of Pharmaceutical Excipients" published by American Pharmacists Association and the Royal Pharmaceutical Society of Great Britain 2006, 132-135pp.
16. RJ Harwood, "hydroxypropyl cellulose" in "Handbook of Pharmaceutical Excipients" published by American Pharmacists Association and the Royal Pharmaceutical Society of Great Britain 2006, 336-340pp.
17. NA Armstrong, "Calcium Carbonate" in "Handbook of Pharmaceutical Excipients" published by American Pharmacists Association and the Royal Pharmaceutical Society of Great Britain 2006, 89-92pp.
18. S Edge, A Kibbe, "lactose" in "Handbook of Pharmaceutical Excipients" published by American Pharmacists Association and the Royal Pharmaceutical Society of Great Britain 2006, 389-395pp.
19. RT Guest, "croscarmellose sodium" in "Handbook of Pharmaceutical Excipients" published by American Pharmacists Association and the Royal Pharmaceutical Society of Great Britain 2006, 211-213pp.