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Der Pharmacia Lettre, 2012, 4 (3):714-719
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Development and *in vitro* evaluation of film coated micronized immediate release tablets of ursodeoxycholic acid

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ABSTRACT

Ursodeoxycholic acid (UDCA) belongs to Biopharmaceutical Classification System (BCS) class II and hence it exhibits low aqueous solubility and high permeability. Solubility of this drug is very low which affects in low dissolution rate and in turn affect the bioavailability of this drug following oral administration. The purpose of the present study is to design an immediate release tablet containing ursodeoxycholic acid by wet granulation technique with help of diluents, superdisintegrants and surfactant. Tablets are analysed for weight variation, thickness, hardness, friability, disintegration time and to compare the drug dissolution profile with USP tolerances limit.

Keywords: BCS Class II, Ursodeoxycholic acid, immediate release tablet, wet granulation, dissolution.

INTRODUCTION

Ursodeoxycholic acid (UDCA) is used in the treatment of cholestatic liver diseases, gallstone dissolution, and for patients with hepatitis C virus infection to ameliorate elevated alanine aminotransferase levels. Mechanisms include the improvement of bile acid transport and/or detoxification, cytoprotection and anti-apoptotic effects^[1, 2, 3].

Ursodeoxycholic acid (UDCA) belongs to Biopharmaceutical Classification System (BCS) class II and hence it exhibits low aqueous solubility and high permeability. It is a white; odorless; crystalline powder with a bitter taste^[4]. Chemically it is 3a, 7a dihydroxy- 5-cholan-24-oic acid (Fig. 1).

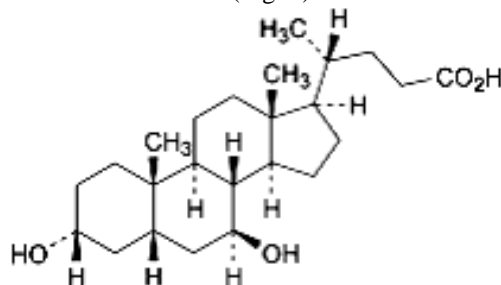


Figure 1: Ursodeoxycholic acid (CAS number:128-13-2)

It is a bile acid; a substance naturally produced by the body that is stored in the gall bladder. It works by decreasing the production of cholesterol and by dissolving the cholesterol in bile so that it cannot form stones^[5, 6, 7]. However; the low aqueous solubility and poor dissolution of this molecule in gastric fluid affects its rate of absorption; resulting in a low and variable oral bioavailability. It is used as a drug for the dissolution of cholesterol gallstones because it reduces the cholesterol saturation of bile^[8, 9]. The use of UDCA for the treatment of other liver

diseases; such as primary biliary cirrhosis; chronic hepatitis and biliary pains has been demonstrated. However in vivo studies have shown that intestinal absorption and consequently the bioavailability of the drug are generally poor and erratic both among different subjects; and within the same subject ^[10]. More than 50% is lost in the stool ^[11] after a single oral dose of 300 mg.

MATERIALS AND METHODS

Materials:

The raw drug UDCA was gifted by Biocon Ltd. Bangalore and the tablet excipients like lactose monohydrate, sodium lauryl sulphate, pregelatinised starch, sodium starch glycolate, povidone K-30, cross povidone, starch, magnesium stearate and all the reagents used were of analytical grade.

Drug –excipient compatibility studies

1) By DSC: The physicochemical compatibilities of the drug and the used excipient were tested by differential scanning calorimetric (DSC) analysis. DSC thermograms of drug alone and mixture of drug and ingredient were derived from a DSC with a thermal analysis data station system

2) By FTIR: The physicochemical compatibilities of the drug and the used excipient were tested by FTIR analysis. IR spectra of the drug alone and drug excipient mixture were compared and correlated.

Particle size of Ursodeoxycholic acid

UDCA were measured by particle size analyzer (Master Sizer 2000 SM; Malvern; UK).

This instrument works on the principle of laser diffraction. The drug particles were dispersed in Milli Q water and used to analyze the particle size. The results were expressed as plots of volume percentage vs. particle size (µm).

Preparation of film coated immediate release tablet:

The immediate release UDCA tablets were done by wet granulation method. The required amount of the drug; Lactose monohydrate; Pregelatinised starch; PVP k-30; Sodium lauryl sulphate and Sodium starch glycolate (super disintegrant) were mixed in geometrical order. Granules were prepared by using starch paste, wet granules pass through sieve no. 10. These granules were dried in the oven to obtain the loss on drying value as 3.2-3.6 % and then sieved through 22 sized mesh ^[12, 13, 14]. The granules after treating with magnesium stearate (antiadherent) and talc (lubricant) were then compressed in 16 stations, single rotary; “D”-Tooling machine of punch size 12 mm. The tablets were then film coated with ethyl cellulose (EC) and hydroxypropyl methyl cellulose (HPMC) mixed with the plasticizer PEG 6000 and titanium dioxide as opacifier. After several trials and evaluation processes the formula of F7 (Table no.1) was found to be suitable and fixed for the wet granulation technique. The selected formula was also used to prepare tablets with the micronized drug ^[15]. The formulated tablets were coated with ethyl cellulose (totally water insoluble and gastric acid pH resistant); hydroxypropyl methyl cellulose (water soluble polymer) in the ratio of 25:1 while PEG 6000 is used as a plasticizer in Electrolab Lab scale Coating Pan (Model: ECP-12) with peristaltic pump- PP-50V. The gain in weights of individual tablets varies from 10-12 mg. Maximum amount of the drug degrades in the acidic gastric pH thus leading to poor bioavailability. To minimize the loss; ursodeoxycholic tablets are coated with polymers ethyl cellulose and HPMC. HPMC acts as pore forming material in the tablet coat.

Table no.1: Composition of all batches of immediate release Ursodeoxycholic acid formulation.

Sr.No.	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
1	Ursodeoxycholic acid	301.00	301.00	301.00	301.00	301.00	301.00
2	Lactose monohydrate	162.00	157.00	99.00	100.00	102.00	100.00
3	Pregelatinised starch	-	-	58.00	67.00	60.00	57.00
4	Sodium starch glycolate	25.00	25.00	25.00	15.00	15.00	16.50
5	PVP k-30	4.50	4.50	4.50	4.50	5.00	5.00
6	Sodium lauryl sulphate	1.00	1.00	1.00	1.00	2.00	3.00
7	Starch (for paste)	19.00	19.00	19.00	19.00	19.00	19.00
8	Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
9	Sodium Starch Glycolate	5.00	10.00	10.00	10.00	13.5	16.00
10	Magnesium Stearate	2.50	2.50	2.50	2.50	2.50	2.50
Total wt.		520.00	520.00	520.00	520.00	520.00	520.00

EVALUATION OF DRUG AND TABLET BLEND**Physical properties of powder and granules:****1) Apparent Density / Bulk Density:**

Bulk density or apparent density is defined as the ratio of mass of a powder to the bulk volume. The bulk density of a powder depends primarily on particle size distribution; particle shape; and the tendency of the particles to adhere to one another.

Procedure: 25g drug was weighed and shifted through ASTM 20# sieve then transfer in 100ml measuring cylinder. Powder was carefully leveled without compacting; and the unsettled apparent volume (V_0) was read. The appearance bulk density in g/ml was calculated by the following formula:

Bulk density = Weight of the Blend / Volume of the packing.

2) Tapped Density:

25g drug was weighed and shifted through ASTM 20# sieve then transfer in 100ml measuring cylinder. The cylinder was kept into the holder of tap density tester. Initial volume V_a and weight of powder was entered on screen of apparatus and was run 500 taps. After 500 taps observed taps volume V_b was entered on screen and again run for 750 taps. If the difference ($V_a - V_b$) was less than 2% then test was discontinued and result was noted from screen without disturbing the cylinder. However, if ($V_a - V_b$) was greater than 2% then test was continued for 1250 taps.

Tapped density = Mass of powder / Tapped Volume.

3) Hausner Ratio:

Hausner ratio gives an idea regarding the flow of the blend. It is the ratio of tapped density to the apparent density. Hausner ratio was calculated as:

HR = Tapped density / Bulk density

4) Compressibility Index:

The compressibility index measures of the propensity of powder to be compressed. The packing ability of drug was evaluated from change in volume; which is due to rearrangement of packing occurring during tapping. It is indicated as Carr's compressibility index (CI) and can be calculated as follows:

CI% = (Tapped density – Apparent density) \times 100 / Apparent density

Physicochemical evaluation of coated tablets:

Hardness, friability, diameter and thickness, weight variation and content uniformity were measured to evaluate physicochemical property of tablets. 15 Tablet hardness were measured by Dr. Schleunigerpharmatron tablet hardness tester and expressed in N. Roche friabilator was used to determine friability of the formulated tablets taking 20 tablets at a time [16]. Thickness was measured by digital slide calipers (Mitutoyo, Japan). The weight variation of prepared coated tablets were determined by taking 20 tablets as per the USP guidelines. 16 Content uniformity of prepared tablets was studied as per the assay method described in the USP 32 – NF 27, First supplement.

In vitro release studies:

The coated tablets prepared with micronized and non-micronized drug were subjected to dissolution study in USP type II apparatus containing the phosphate buffer of pH 8 with paddle speed of 75 rpm at a constant temperature of $37 \pm 0.5^\circ\text{C}$. The drug released in the dissolution medium was analysed at 15, 30, 45 and 60 minutes. The drug release from the tablets was quantified in HPLC using refractive index detector of sensitivity 64 at 40°C using C8 column and mobile phase comprising 0.1% v/v acetic acid solution and methanol in the ratio of 300:700 with a flow rate of 1.5 mL/min [17, 18]. The retention time of the drug came around 7.5 minutes. There was no interference of the ingredients of prepared tablet in HPLC analysis. Six replicates of each tablet were taken for the in vitro dissolution study and the cumulative percentage release was tabulated in Table no.5.

Stability studies:

Final optimized formulation was kept for stability studies for 3 months under conditions recommended by ICH guidelines at $40^\circ\text{C}/75\%\text{RH}$, $30^\circ\text{C}/65\%\text{RH}$ and checked for physical parameters and in vivo drug release profile.

RESULTS AND DISCUSSION

Drug excipient interaction:

1) For DSC: Fig. 2 A shows DSC thermograms of drug alone and Fig. 2 B shows DSC thermograms of mixture of drug and ingredient. Thus; it was thought to indicate that there was no evidence of interactions between drug and excipient used in study.

2)

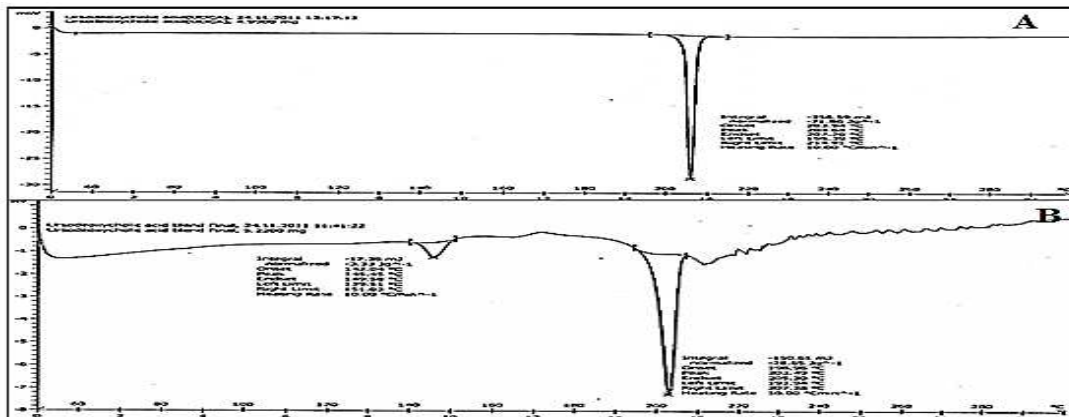


Figure 2: A- DSC thermograms of drug alone and B- DSC thermograms of mixture of drug and ingredient.

3) For FTIR: Figure 3 shows FTIR spectrum of sample (drug excipient admixture) which was compared with std. spectrum of drug and groups assigned were checked. Thus it was concluded that there was no interaction between drug and excipient used.

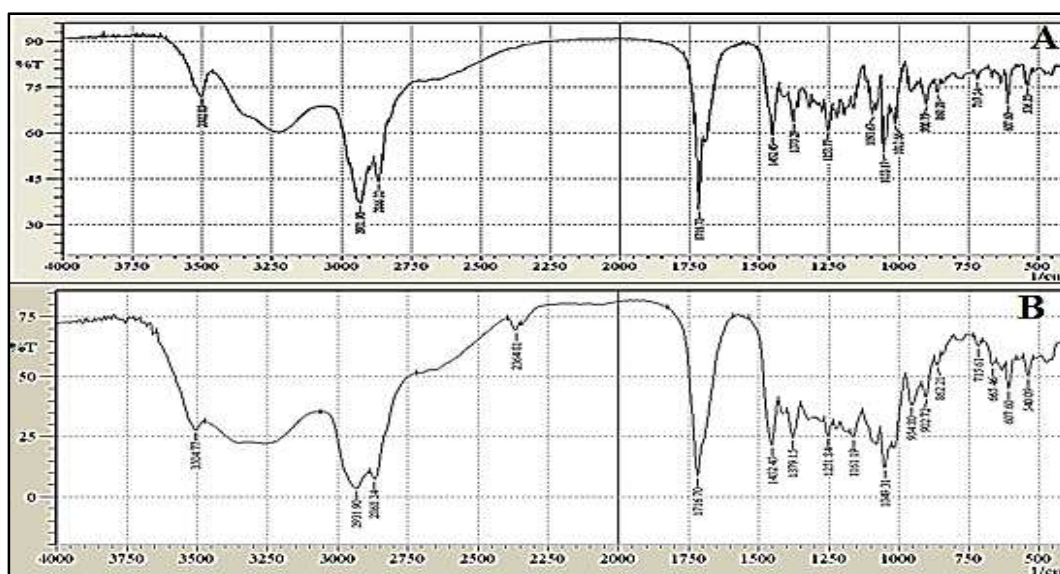


Figure 3: A- FTIR of drug alone and B- FTIR of mixture of drug and ingredient.

Particle size of Ursodeoxycholic acid

The particles were distributed in different range of sizes (10 μ to 30 μ).

Physical properties of powder and granules

The present compressibility of drug was 44.59% indicating its poor flow ability of powder suggesting that it should be granulated prior to compression. Physical properties of drug are shown in Table no. 2 and properties of granules ready for compression (GRC) of respective batches are shown in Table no. 3.

Table no.2: Physical properties of drug

INGREDIANTS	BULK DENSITY (g/mL)	TAPPED DENSITY (g/mL)	% COMPRESSIBILITY INDEX	HAUSNER RATIO
URSODEOXYCHOLIC ACID	0.378	0.682	44.594	1.805

Table no.3: Physical properties of granules ready for compression (GRC)

Batch no.	Bulk density(g/ml)	Tapped density (g/ml)	% Compressibility index	Hausner ratio	LOD %
F1	0.51	0.62	17.02	1.20	2.36
F2	0.48	0.63	21.80	1.24	2.53
F3	0.54	0.64	20.35	1.25	2.45
F4	0.53	0.65	18.46	1.22	2.32
F5	0.49	0.62	20.09	1.23	2.13
F6	0.59	0.72	18.05	1.22	2.65

Physicochemical evaluation of coated tablets:

Results of different physiochemical property evaluation were described in the Table no.4.

Table no.4:Physicochemical properties of all batches

Batch no.	Weight variation (mg)	Thickness (mm)	Hardness (N)	Friability (%)	Disintegration time (min.)	Drug content (%)
F1	520.00	4.26	45	0.054	7	97.78
F2	523.00	4.35	49	0.075	6	99.54
F3	522.00	4.28	45	0.088	6	98.18
F4	520.00	4.32	46	0.046	6	99.57
F5	522.00	4.21	48	0.069	4	98.37
F6	521.00	4.23	45	0.095	3	99.46

In vitro release studies:

Table no.5:In vitro dissolution study of ursodeoxycholic acid in formulation

Time	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
15	25.67	31.45	34.65	35.12	39.69	45.98
30	53.98	58.12	59.71	63.32	67.92	74.54
45	72.23	74.43	76.56	80.67	83.76	89.65
60	85.43	86.34	87.67	89.24	94.56	99.45

STABILITY STUDIES

Results for stability studies for 3 months under conditions recommended by ICH guidelines at 40°C/75%RH, 30°C/65%RH checked for physical parameters and in vivo drug release profile. Hardness of the tablets was within the range of 45-50 N. All formulations were compliant with official compatibility; which allow not more than 1% of mass lost on 20 tablets weight. Weight variation and thickness; studied with all batches of tablet were within the satisfactory limit. The content of the drug in the tablets were within the acceptable range.

CONCLUSION

Six formulations of Ursodeoxycholic acid were prepared with varying concentration of Sodium starch glycolate, PVP k-30, Sodium lauryl sulphate as surfactant, Lactose monohydrate and Pregelatinised starch was used as diluents (Table 1). For each formulation, granules were prepared and evaluated for various parameters as explained earlier. The drug material shows poor flow properties so wet granulation method is used to improve flow properties. Bulk density, was found in the range of 0.480-0.591 g/cm³ and the tapped density between 0.620-0.720 g/cm³. Using these two density data hausner's ratio and compressibility index was calculated. The granules of all formulations had hausner's ratio less than 1.25 indicates better flow property. The compressibility index was found between 17.02-21.80 % which indicates a fairly good flowability of the granules. The drug content was found in the range of 97.78 %-99.57 % (acceptable limit) and the hardness of the tablets were found below 1% friability indicating a good mechanical resistance of the tablets, and the parameters were found well within the specified limit for uncoated tablets. The in-vitro disintegration time (DT) of the tablets was found to be between 3-7 min. Tablets of batch no. F6 which contains 6.25% Sodium Starch Glycolate and 0.57% of sodium lauryl sulphate (surfactant) should show disintegration time of 3 min and showing 99.45% drug release in 60 min (acceptable limit). It was concluded that immediate release tablets of Ursodeoxycholic acid can be successfully prepared selected superdisintegrants and surfactant in order to improve disintegrants/dissolution of the drug for better patient's compliance & effective therapy.

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