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Focus

Vitamin A

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Vitamin A is known to exist in two molecular structures designated as vitamin A_1 and vitamin A_2. Vitamin A_1 known as retinol is an "all-trans" compound. Vitamin A_2 is "3-Dihydroretinol". All the synthetic vitamin A are derivatives of retinol only. As is well known, vitamin A is available in plenty from animal sources; liver being a rich source. Fish liver oils are important natural sources of vitamin A. While fish liver oil obtained from the sea-fish contains vitamin A_1 only, the sweet-water-fish-liver-oil contains both A_1 and A_2. However, pure vitamin A is made by synthetic methods. Deficiency of vitamin A in men and animals is manifested by drynesss in skin, retarded growth in children and night blindness, in general, as the early symptoms which is aggravated to conjunctivitis of the eye and finally to total blindness in severe deficiency. The normal dietary requirements of vitamin A vary with age, and sex and are usually about 2,500 to 3,500 IU for children (below 12 years) and about 4,500 to 5,000 IU for adults.

2. Demand:

Total availability figures computed from the indigenous production and imports into the country show vitamin A having had a compound growth rate of about 12% from 1970-71 to 1979-80. The growth rate has shown an increase during the recent years from 1977-78 onwards. With the normal availability of vitamin A at slightly over 50 MMU during 1977-78, reports of shortage in the country came to surface for the first time after about seven years. On the basis of the appraisal of the situation prevailing during the last 3 years, the demand of vitamin A during 1977-78, 1978-79 and 1979-80 could be placed at 60 MMU, 70 MMU and 80 MMU respectively, although the actual availability was 50.2 MMU, 77.2 MMU and about 96 MMU respectively. In the projection of future demand it is expected, that the following would be the demand of vitamin A during the next 5 years:—

Year	*Quantity in MMU*
1980-81	100
1981-82	115
1982-83	130
1983-84	150
1984-85	170

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3. Supply:

The following is the capacity break-up, approved as on date, for the basic production of vitamin A:

Name of the Company	Unit	Approved Capacity IL*	LI**	Total
1. Roche Products Ltd, Bombay	MMU	15	—	15
2. Glaxo Laboratories Ltd, Bombay	„	30	—	30
3. Kerala State Drugs & Pharmaceuticals Ltd, Alleppey	„	30	—	30
				75

* Industrial Licence; ** Letter of Intent.

The supply of vitamin A through indigenous production during the last 3 years had been as under:

1977-78	50.2 MMU
1978-79	62.2 „
1979-80	58.8 „

Imports during the same period had been nil, 15 MMU and 37 MMU respectively.

Of the three units, approved for manufacture of the item, only Roche and Glaxo are in production. Kerala unit is expected to come into production by the middle of 1981-82. If everything goes well, the total availability of vitamin A through indigenous production from the two producing units during this year (1980-81) would be of the order of 60-65 MMU. This would leave a gap of about 35-40 MMU which would need to be imported. Next year (1981-82), if Kerala unit comes into production, the indigenous production may reach, at best, a level of 75-80 MMU which would again necessitate imports of substantial quantity of the item. Prediction of the situation beyond 1981-82 would not be much meaningful at this stage.

4. Growth:

Past (1970-71 to 1979-80) average about 12% (compound) per year. Future (1980-81 to 1984-85) expected around 13-15% (compound) per year.

5. Price:

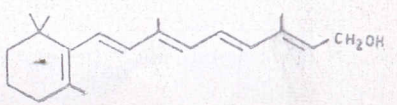
Vitamin A is available commercially in bulk form as retinol acetate and palmitate, diluted in refined vegetable oil with added stabilisers. The price, controlled by the Government, is Rs. 562 00 per 1,000 MIU for both acetate and palmitate. Other commercial forms are: admixed with emulsifiers and stabilisers and packed in dry form which when reconstituted is miscible with water; coated with gelatine and sugar and packed dry and mixed with vitamin D_3 and other viamins like E, C and K etc.

6. Consumption/Use:

Bulk vitamin A is consumed in a major way in the production of various drug formulations; nearly 35 to 40 MMU annually is consumed in the manufacture of various drug formulations representing nearly 65 to 70% of the total availability of vitamin A. Besides a substantial quantity of the order of 14 to 17 MMU (30-35%) goes in for enriching hydrogenated oil in the vanaspati industry as per the statutory requirements.

7. Important production techniques of vitamin A (Retinol):

The following is the accepted structure for retinol:



As this molecule conatains five double bonds it could, therefore, exist in thirty two different geometrically isomeric forms. However, it is the "all-trans" isomer which is desirable, because all the other known isomers have less activity than the "all-trans" isomer. At the moment only six isomers have been isolated of which, only four are naturally occurring ones. The six isomers which have been isolated are:

(*i*) The "All-trans" retinol (activity 100%),

(*ii*) 13-cis-7,9,11-tri-trans-retinol also called Neovitamin Aa (activity 75%)

(*iii*) 9-mono-cis 7,11,13 tri-trans-retinol also called Isovitamin Aa (activity 25%)

(*iv*) 9,13 di-cis-7,11-di-trans-retinol also called Isovitamin Ab (activity 25%)

(*v*) 11-cis 7,9,13-tri-trans-retinol also called Neovitamin Ab (activity 25%)

(*vi*) 11,13-di-cis-7,9-di-trans-retinol also called Neovitamin Ac (activity 25%)

Since the "all-trans" retinol is the desired isomer, great care has to be taken to ensure that only this isomer is formed during the synthesis. As a matter of history it is important to mention that vitamin A was synthesised for the first time by R. Kulin & C. J. R. Morris (*Ber.*, **70**, 853, 1937); the synthesised material had, however, only about 7.5% of the vitamin A activity. Obviously, the material was impure; it could be that it was also contaminated largely with less active isomers.

At present, the industrial methods of synthesis follow the routes, propounded largely by O. Isler *et. al* [(*i*) *Experientia*, **2**, 31, *1946*; (*ii*) *Helv. Chim. Acta*, **30**, 1911 *1947*; (*iii*) *Helv. Chim. Acta..*, **32**, 489, *1949*; (*iv*) *Chimia* (*Aarau*), **4**, 103 *1950*], wherein an aldehyde, commonly known as "C_{14}-aldehyde", is initially synthesised using betaionone as the starting material.

Dargen's condensation of betaionone with monochloro-methyl acetate in strongly basic conditions gives "C_{14}-aldehyde" through an intermediate epoxide. C_{14}-aldehyde thus obtained is reacted with ethyl magnesiumbromide treated 1-pentol in an organic solvent to get a product, commonly known as 'oxenine'. The latter is selectively reduced at the acetylenic double bond with hydrogen using quinoline poisoned palladium catalyst, to get a product known as hydronynine. The latter containing one primary and one secondary hydroxyl group is selectively acetylated at the primary alcoholic centre followed by dehydration and rearrangement in presence of a strong acid to get vitamin A acetate. Trans-esterification of the product with ethyl palmitate would give vitamin-A palmitate.

A slight modification of the above routes was published in: (i) U.S. Pat. no. 2, 369, 156 by N. A. Milas, *1945*, and (ii) N. A. Milas, *Science*, **103**, 581, 1946. Several other methods having some or major modification of the above have been described in the following references: (1) W. Oroshink, *J. Amer. Chem. Soc.*, **67**, 1627, *1945*; (2) J. F. Arens, D. A. Van Dorp, *Nature*, **157**, 190, *1946*; (3) J. F. Arens, D. A. Van Dorp, *Nature*. **160**, 189, *1947*; (4) J. F. Arens, D. A. Van Dorp, *Rec. Trav. Chim.*, **65**, 338, *1946*; (5) O. Schwarzkopf, H. J. Cahnmann, A. D.

Lewis, J. Swidinsky, H. M. Wuest., *Helv. Chim. Acta.*, **32**, 443, *1949*; (6) H. Linder, *Helv. Chim. Acta.*, **35**, 446 *1952;* (7) H. Pommer, *Angew. Chema*, **72**, 811, *1960*) using betaionone as the starting material. Another method studied extensively was the condensation of betaionone with the ethylester of 6-bromo 3-methyl hex-2-en-4-yoic acid by the Reformatsky reaction. The condensation product was subjected to dehydration, followed by selective hydrogenation at the acetylinic double bond to give ethylester of retinoic acid, which on reduction gave retinol.

The starting material for all the above synthesis had been betaionone; there are several methods for its synthesis. However, in our country none other than citral could be found to be a commercially suitable method for its synthesis. Lemongrass, grown extensively in India, specially in far-south in Cochin, on steam distillation gives an oil, commonly known as Lemon Grass Oil (L. G. O.) which contains 75-80% of citral in it. In effect, therefore, L. G. O. forms a starting material for betaionone.

Several other routes of synthesis without the use of betaionone have been reported, noteworthy among them was that reported by J. Attenburrow, A.F.B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.*, 1094, *1952*] to start from 2, 2, 6 trimethylcyclohexanone. Several other interesting routes have also been investigated and an inquistive reader may like to go through them; (1) G. Wittig and U. Schllkopf *Ber.*, **87**, 1318, *1954* (2) U. Scholkopf, *Angew. Chem*, **71**, 260 *1959*, (3) H. Pommer, *Angew. Chem.*, **72**, 260, *1960*, (4) S. Trippett, *Advances in Organic Chemistry, Methods and Results* (*Ed.* by R. A. Rapheal, E. C. Taylor & H. Wynberg), Vol. 1, Interscience Publishers 1960, (5) S. F. Dyke, *The Chemistry of the Vitamins*, Vol-VI, 1965, Interscience Publishers). Since such methods are usually of academic interest and have limited commercial application in our country at this juncture I have refrained from dealing with them in this write-up.

8. Demand and Supply :

Blindness due to inadequate vitamin A intake is a matter of serious concern as every year nearly 10,000-12,000 children fall prey to blindness in India. To overcome this, the vitamin is being distributed by Government through various channels for quite some time. It is expected that this national programme will be intensified which would result in increased consumption.

Vitamin A is also used extensivdy in multivitamin preparations. The market for such preparations is increasing fast and it is expected that the trend will be maintained. Thus nearly 35-40 MMU of the vitamin representing 65-70% of the total available is consumed in the manufacture of various drug formulation.

A large amount of vitamin A is used for enriching hydrogenated oils under statutory orders. It is estimated that the vegetable oil industry must have consumed at least 14.25, 17 and 15.5 MMU respectively during the last three years. Based on the projected increase of hydrogenated oil production during 1980-81 and 1984-85, the consumption of the vitamin by the vanaspati industry will be of the order of 18 MMU in 1980-81 and 22 MMU in 1984-85. Due to various reasons, the potency of vitamin A in

hydrogenated oil decreases very fast, and therefore to maintain the level required by the Statutory Order, the manufacturers may have to add large excess of the vitamin.

Thus it is expected that the demand will increase steadily in the coming years and this can not be fully met with indigenous production. From the estimated demand figures, it appears that even after the Kerala unit comes into full production and assuming that the two existing producers come up to full installed capacity, a large gap of 65-70 MMU would develop by 1984-85. However, if imports are liberalised as a consequence, indigenous production may suffer. It would, therefore, be desirable to create additional capacities either by expansion of existing units or by establishing new units. A new unit of 65-70 MMU capacity will have benefit of the economics of production and will not be large enough to face problems of marketing the product. The advantages are expected to be larger if such capacity is created by expansion of existing units. Since capacity of this size would take some time to create, an expeditious decision in this regard is required.

As per the New Drug Policy, vitamin A is open for licencing to all sectors of the industry and, therefore, there is no restriction in procuring technology even from outside. In the choice of a technology, petroleum based starting materials would be more expensive, under Indian conditions, compared to agriculture based materials. Processes starting from betaionone would be more appropriate because it accounts for more than one-third of the material cost of vitamin A production and can be made from lemon grass oil which is produced commercially in the country.