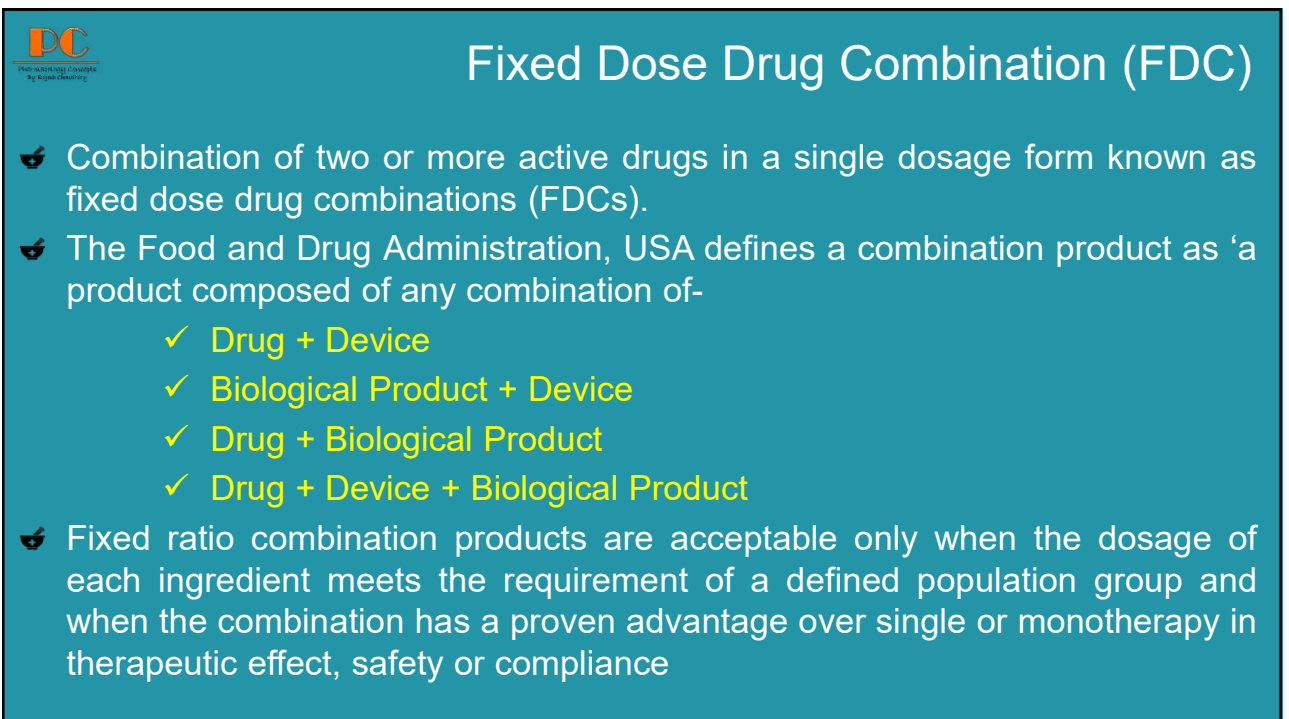


PC  
Pharmacology Concepts  
By Rajesh Choudhary

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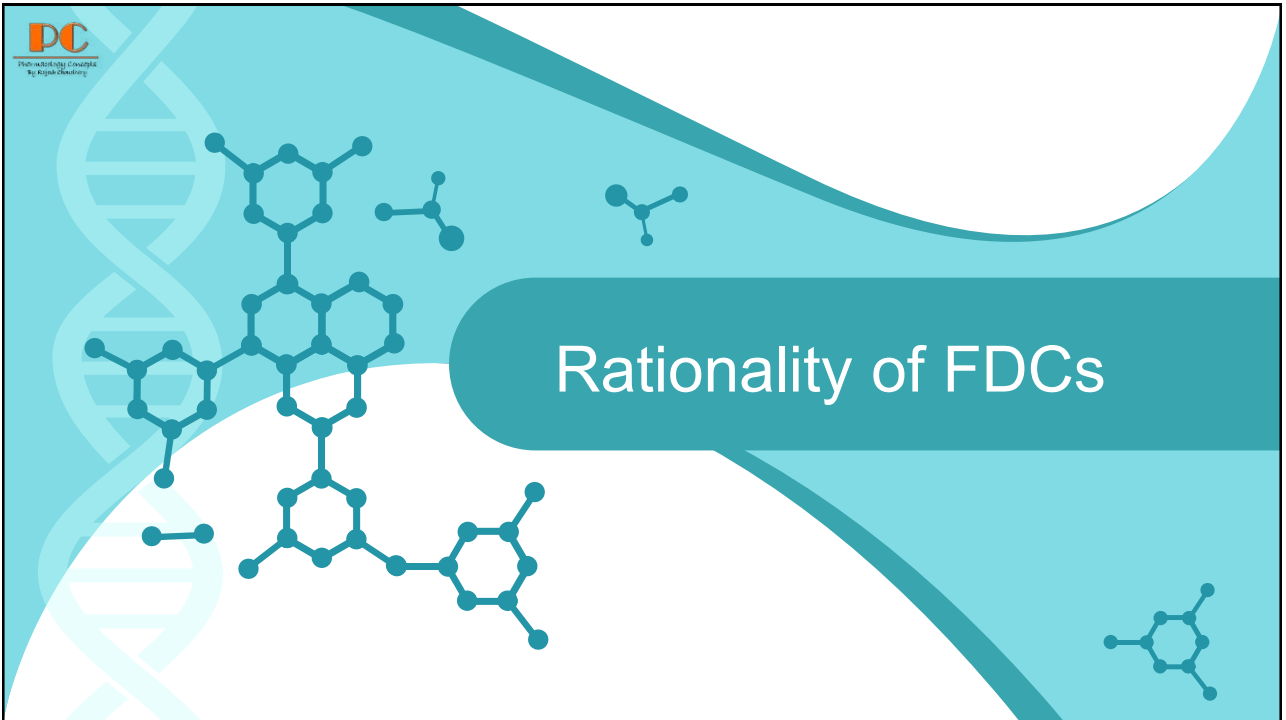
Rational to  
Combination Therapy  
Fixed Dose Drug Combination (FDC)



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By Rajesh Choudhary

## Fixed Dose Drug Combination (FDC)

- ✎ Combination of two or more active drugs in a single dosage form known as fixed dose drug combinations (FDCs).
- ✎ The Food and Drug Administration, USA defines a combination product as 'a product composed of any combination of-
  - ✓ Drug + Device
  - ✓ Biological Product + Device
  - ✓ Drug + Biological Product
  - ✓ Drug + Device + Biological Product
- ✎ Fixed ratio combination products are acceptable only when the dosage of each ingredient meets the requirement of a defined population group and when the combination has a proven advantage over single or monotherapy in therapeutic effect, safety or compliance



**PC**  
Pharmaceutical Company  
by Alpha Chemicals

## Rationality of FDCs

The rationality of FDCs should be based on certain aspects such as

1. The drugs in the combination should act by different mechanisms
  - ✎ E.g. **FDC- Amlodipine (5 mg) + Atenolol (50 mg)**
  - ✎ Amlodipine- CCB & Atenolol-B Blocker
2. The pharmacokinetics must not be widely different
  - ✎ Both have approximately similar t-half and Vd.
  - ✎ E.g. **FDC- Amoxicillin (500 mg) + Clavulanic acid (125 mg)**. Amoxicillin (t<sub>1/2</sub>= 1-2 h & Vd= 0.21 L/kg) + Clavulanic acid (t<sub>1/2</sub>= 1-1.5 h & Vd= 0.2 L/kg).
3. The combination should not have supra-additive toxicity of the ingredients.

## Advantages of FDCs

The rationality of FDCs should have advantages over monotherapy:

- Convenience in dose schedule and administration for the patients.
- FDCs enhance the effects by synergism
- FDCs enhance the therapeutic efficacy and therapeutic benefits
- FDCs reduces the side effects
- FDCs can improve compliance in the treatment of chronic infective diseases like TB and HIV

## Rational FDCs

The rational FDCs are:

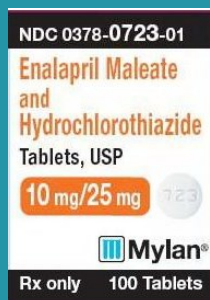
- L-dopa (200 mg) + Carbidopa – **Antiparkinsonian FDCs**
- Aceclofenac (100 mg) + Paracetamol (325 mg) + Tramadol (37.5 mg) – **Analgesic and Antipyretic**
- Amoxycillin (500 mg) + Clavulanic Acid (125 mg) - **Antibiotics**

<p>NDC 16729-079-10</p> <p><b>Carbidopa and Levodopa Extended-Release Tablets</b></p> <p><b>50 mg/200 mg</b></p> <p><b>Rx Only</b></p>	<p><b>Aceclofenac, Paracetamol &amp; Tramadol Tablets</b></p> <p><b>PACTODOL</b></p> <p><b>2 X 5 X 10 Tablets</b></p> <p>SCHEDULE 'H' DRUG WARNING : To be sold by retail on the prescription of a Registered Medical Practitioner only.</p> <p>Each film coated tablet contains:            Aceclofenac IP 100 mg,            Paracetamol IP 325 mg,            Tramadol Hydrochloride IP 37.5 mg,            Excipients: q.s.</p> <p>Colour: Quinoline Yellow</p> <p>Dose : As directed by the physician            Keep out of reach of children.</p> <p>Store in dry place at a temperature below 30°C.</p> <p><b>WEST-COAST</b>            Pharmaceutical Works Ltd.            Plot No. 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 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tablets</b></p> <p>Each film-coated tablet contains :            Amoxycillin Trihydrate IP equivalent to Amoxycillin 500 mg            Potassium Clavulanate IP            (as Potassium Clavulanate Diluted IP)            equivalent to Clavulanic Acid 125 mg</p>
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## Rational FDCs

- ✦ Enalapril (10 mg) + Hydrochlorothiazide (25 mg)- **Antihypertensive**
- ✦ Rifampicin (150 mg) + INH (75 mg) + Pyrazinamide (400 mg) + Ethambutol (275 mg)- **Anti TB**
- ✦ Efavirenz (600 mg) + Emtricitabin (200 mg) + Tenofovir (300 mg)- **Anti HIV**



## Irrationality of FDCs

## Disadvantages of FDCs

### The Disadvantages of FDCs:

- ✘ Dose cant be adjusted independently.
- ✘ If some ADRs are observed, it becomes difficult to identify one particular drug which is causing harmful effects
- ✘ Pharmacokinetic properties of both drugs must be similar.  
Different in pharmacokinetic profile, changes the frequency of administration of individual drug
- ✘ FDCs should not be harmful drug interaction
- ✘ Some combination increase the ADR (Nimesulide + paracetamol)

## Disadvantages of FDCs

### The Disadvantages of FDCs:

- ✘ Unnecessary combination increase the price (Ibuprofen + paracetamol + caffeine)
- ✘ Inappropriate FDC becomes a dangerous (CCB + Digitalis-cardiac arrest)

Irrational FDCs are:

- ✘ Nimesulide + paracetamol – increase Hepatotoxicity
- ✘ Rebeprazole + Domperidone- Increase Rhabdomyolysis
- ✘ Ranitidine + Dicyclomine – acidic gastric pain is control by H2 blocker (ranitidine) only, No need to added antispasmodic (Dicyclomine)

### Recommendation for FDCs

As per WHO expert committee, FDCs should be only used when there are no alternative of single drug is available or Therapeutic benefit or cost effective for the purpose





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