FORMULATION AND EVALUATION OF ACETAMINOPHEN AND METHOCARBAMOL BILAYERED TABLETS

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ABSTRACT
The best new therapeutic entity in the world is of little value without an appropriate delivery system. Tablet delivery system can range from simple immediate release formulations to complex extended or modified release dosage forms. The most important role of drug delivery system is to get the drug delivered to the site of action in sufficient amount & at the appropriate rate. However it should meet other important criteria such as physical & chemical stability, ability to be mass-produced in a manner that assures content uniformity. Oral rouse is the most convenient and commonly used method of drug delivery. More than 50% of drug delivery systems available in the market are oral drug delivery systems. They offer convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost. Pharmaceutical oral solid dosage forms have been used widely for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules.

KEYWORDS: Methocarbamol, Acetaminophen,FDC, Bilayered tablets.

INTRODUCTION:

TABLET

Definition: Tablets are tamperproof solid unit dosage forms containing medicament or mixture of medicaments and excipients compressed or molded into solid cylindrical shape having either flat or convex surfaces.

ADVANTAGES AND DISADVANTAGES:

Advantages:

- Offers greatest capability of al oral dosage forms for the greatest dosage precision & least content Uniformity.
- High patient compliance.
- Their cost is lowest of all dosage forms
- Easiest and cheapest to packaging and shipment
- They are having best combined properties of chemical, mechanical and microbiological properties.

Disadvantages:

- Some drugs resist compression owing to their amorphous nature & low density character.

- Drugs with poor wetting, slow dissolution property, large dosages or any combination of these features may be difficult or impossible to formulate & manufacture as a tablet.

Types and classes of tablets:

Tablets are classified by their route of administration or function, by the type of drug delivery system they represent within that route, by their form and method of manufacture.

Tablets ingested orally

1. Compressed tablets (CT)
2. Multiple compressed tablets (MCT)
   a. Layered tablets – Bi-layer tablets
   b. Compression coated tablets
3. Repeat action tablets
4. Delayed action and enteric coated tablets
5. Sugar and chocolate coated tablets
6. Film coated tablets
7. Air suspension coated tablets
8. Chewable tablets

Tablets used in oral cavity

1. Buccal tablets
2. Sublingual tablets
3. Troches, Lozenges and dental cones

Tablets used to prepare solution

1. Effervescent tablets
2. Dispensing tablets (DT)
3. Hypodermic tablets (HT)
4. Tablet triturates (TT)

SOLID DOSAGE FORMS

Solid dosage forms are widely prevalent due to their age-old application. Especially, oral solid formulations hold a high potential as they serve to be most convenient for the administration of drugs. These have been developed into a wide range of formulations from conventional dosage forms for immediate release of the drug to controlled release dosage forms for the constant rate of drug release. Oral rouse is the most convenient and commonly used method of drug delivery. More than 50% of drug delivery systems available in the market are oral drug delivery systems. They offer convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost. Pharmaceutical oral solid dosage forms have been used widely for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules.

FIXED DOSE COMBINATION (FDC)

Definition:-"A combination of two or more actives in a fixed ratio of doses."[1]

Examples of FDCs in WHO's list of essential drugs[2]

Anti- Infective: Sulfamethoxazole + Trimethoprim
Anti-Tuberculosis: Rifampicin + Isoniazid
Antiviral: Stavidine + Lamivudine + Neviparine
Antimalarial: Artesunate + Amodiaquine

Example of some Challenges in Development of FDCs[2]

Problems…	*Solutions…*
❖ **Disproportionate doses** **e.g. Metformin + Glibenclamide (400 mg + 2.5 mg)** **- Content uniformity** **- Assay**	✓ **Dilution for low dose drug** ✓ **Drug loading / Adsorption on excipients**
❖ **Different release kinetics** **e.g. Rabeprazole + Domperidone (20 + 30 mg)**	✓ **IR +SR (Use of OCRS)** ✓ **Bilayer/ Trilayer**
❖ **Hygroscopicity** **e.g. Metformin + Glipizide** **Metformin**- Poorly compressible Needs residual moisture **Glipizide** - Degrades in moisture	✓ ***Separate granulation*** ✓ ***Coat the Glipizide particles***
❖ **Altered solubility/ stability** **e.g. Atorvastatin + Ramipril + Aspirin** Synergistic action **Atorvastatin** -is acid labile **Aspirin**- Undergoes alkaline hydrolysis	✓ ***Suitable excipients***

Drug Delivery Systems for FDCs

There are three categories under this class:

I. Layered tablets – two to three component systems.

II. Compression coated tablets – tablet within a tablet.

III. Inlay tablet – coat partially surrounding the core.

The layered tablet is preferred over compression coated tablet as the surface contact is less and the production is simple and more rapid.

Bilayer Tabletting

- ✓ Release of both drugs starts immediately
- ✓ Ease of manufacturing
- ✓ Elegance to the product

Figure-1

Trilayer tabletting

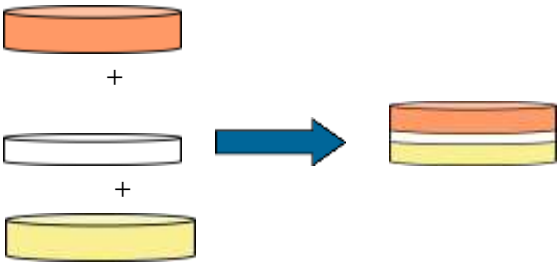


Figure-2

- ✓ Combination of incompatible drugs
- ✓ Combination of different release profiles
- ✓ Elegance to the product

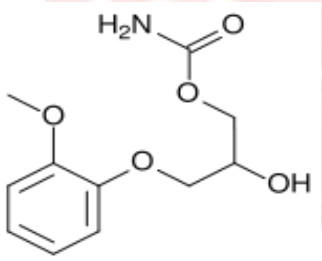
Problems in layered tablets[3]:

- ❖ Lack of proper bonding of two layers
- ❖ Stress due to high compression force degrades certain actives e.g. Ramipril.

DRUG PROFILE

METHOCARBAMOL:

Methocarbamol is a skeletal muscle relaxant, for use as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions.



Methocarbamol

[2-hydroxy-3-(2-methoxyphenoxy)-Propyl] aminoformate][7]

Mechanism of Action:

The mechanism of action of Methocarbamol in humans has not been established, but may be due to central nervous system depression. It has no direct action on the contractile mechanism of striated muscle, the motor end plate or the nerve fiber.

Chemistry: A centrally acting muscle relaxant related structurally to Guaifenesin, Methocarbamol occurs as a fine, white powder with a characteristic odor. In water, it has solubility 25 mg/ml. The pH of commercial injection is approximately 4-5.[7]

Pharmacokinetics - Limited pharmacokinetic data is available in veterinary species. In humans, Methocarbamol has an onset of action of about 30 minutes after oral administration. Peak levels occur

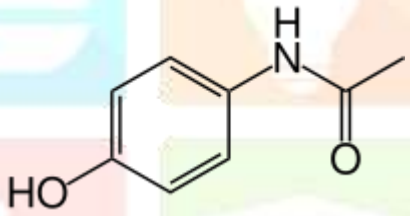
approximately 2 hours after dosing. Serum half-life is about 1-2 hours. The drug is metabolized by dealkylation & hydroxylation.The inactive metabolites are excreted in the urine and in the faeces (small amounts). Guaifenesin is a minor metabolite of Methocarbamol.[8,9]

ACETAMINOPHEN:

Paracetamol or Acetaminophen is the active metabolite of phenacetin, a so-called coal tar analgesic. It is an effective substitute for aspirin, due to its analgesic and antipyretic properties. However, unlike aspirin, it is not a very effective anti-inflammatory agent. It is well tolerated, lacks many of the side effects of aspirin, and is available over-the-counter, so it is commonly used for the relief of fever, headaches, and other minor aches and pains. Paracetamol is also useful in the management of more severe pain, where it allows lower dosages of additional non-steroidal anti-inflammatory drugs (NSAIDs)[4,5,6] or opioid analgesics to be used, thereby minimizing overall side effects. It is a major ingredient in numerous cold and flu medications, including Tylenol and Panadol, among others. It is considered safe for human use at recommended doses, however, acute overdose can cause fatal hepatic damage, and the number of accidental self-poisonings and suicides has grown in recent years

The words acetaminophen and paracetamol both come from the chemical names for the compound: *N*-**acet**yl-para-**aminophen**ol and **par**a-**acet**yl-**am**ino-phen**ol**. In some contexts, it is shortened to **APAP**, for *N*-**a**cetyl-**p**ara-**a**mino**p**henol.[7]

Figure-2



Paracetamol

Mechanism of Action:

Acetaminophen is thought to act primarily in the CNS, increasing the pain threshold by inhibiting both isoforms of cyclooxygenase, COX-1 and COX-2, enzymes involved in prostaglandin (PG) synthesis. Unlike NSAIDs, acetaminophen does not inhibit cyclo-oxygenase in peripheral tissues and thus, has no peripheral anti inflammatory effects. While aspirin acts as an irreversible inhibitor of COX and directly blocks the enzyme's active site, studies have found that acetaminophen indirectly blocks COX, and that this blockade is ineffective in the presence of peroxides. This might explain why acetaminophen is effective in the central nervous system and in endothelial cells but not in platelets and immune cells which have high levels of peroxides. Studies also report data suggesting that acetaminophen selectively blocks a variant of the COX enzyme that is different from the known variants COX-1 and COX-2. This enzyme is now referred to as COX-3. Its exact mechanism of action is still poorly understood, but future research may provide further insight into how it works.[8,9]

Metabolism:

Paracetamol is metabolized primarily in the liver, where its major metabolites include inactive sulfate and glucuronide conjugates, which are excreted by the kidneys. Only a small, yet significant amount is metabolized via the hepatic cytochrome P450 enzyme system (specifically CYP2E1 and CYP1A2), which is responsible for the toxic effects of paracetamol due to a minor alkylating metabolite (N-acetyl-p-benzo-quinone imine, abbreviated as NAPQI). There is a great deal of polymorphism in the P450 gene. Genetic polymorphisms in CYP2D6 have been studied extensively. The population can be divided into "extensive

metabolizers" and "poor metabolizers" depending on their levels of CYP2D6 expression. Depending on the drug effects this could be an area of interest for the patient. If the compound produces a toxic metabolite when metabolized by the P450 system, being an "extensive metabolizer" could lead to adverse effects, whereas being a "poor metabolizer" of a compound whose clearance depends mainly of the P450 system could as well produce adverse effects. NAPQI is a highly reactive compound that can lead to formation of protein adducts oxidative stress, and toxicity. The metabolism of paracetamol is an excellent example of toxication, because the metabolite NAPQI is primarily responsible for toxicity rather than paracetamol itself.[8]

MARKETED SAMPLE

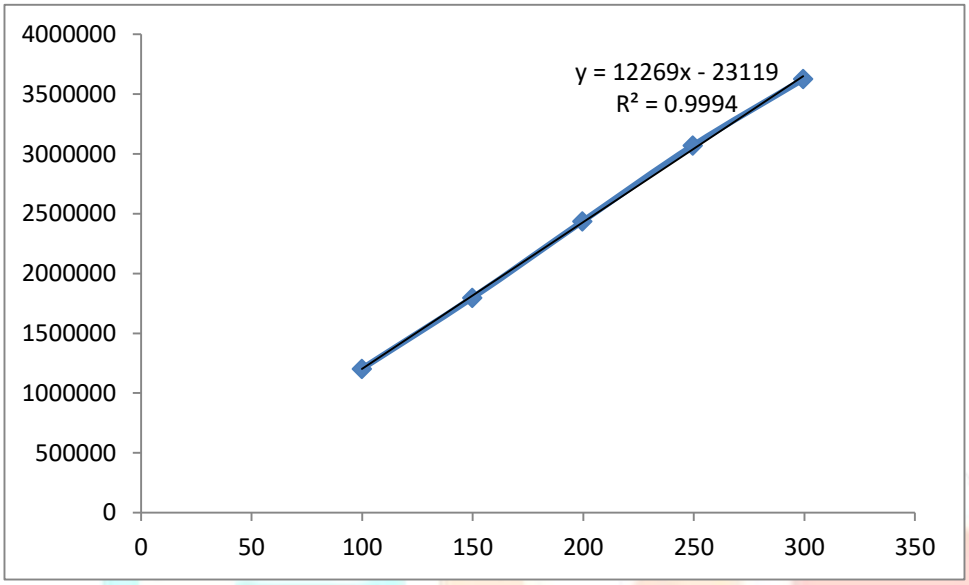
S. No	Name of the material	Specifications	Use	Name of the supplier
1.	Acetaminophen	USP	Pain reliever, antipyretics	Granule's India Limited
2.	Methocarbamol	USP	Skeletal muscle relaxant	Granule's India Limited
3.	Pregelatinised starch	USP NF	Filler and binder	m/s Roquette France Ltd.
4.	Microcrystalline cellulose102	USP NF/ Ph.Eur	Diluents	Mingral chemicals.co.ltd.
5.	Povidon k-30	USP NF/Ph.Eur	Binder	ISP
6.	Sodium luaryl Sulphate	USP NF/Ph.Eur	Wetting agent	Pragna Organics
7.	Sodium starch glycolate	USP NF/Ph.Eur	Disintregent	Yung Zip chemicals India,co.Ltd
9.	Colloidal silicon di oxide	USP NF/Ph.Eur	Glidant	MIS cabot ltd.
10.	Magnesium stearate	USP NF/Ph.Eur	Lubricant	Nitika chemicals
11	Stearic acid	USP NF/Ph.Eur	Lubricant	Nitika chemicals
12.	D&C Yellow	IH	Colouring agent	Roha Dyechem pvt.ltd.
13.	FD&C Blue	IH	Colouring agent	Roha Dyechem pvt.ltd.

ANALYTICAL METHODS

Standard graph of Acetaminophen:

Concentration	Absorbance
99.83	1202025
149.74	1795911

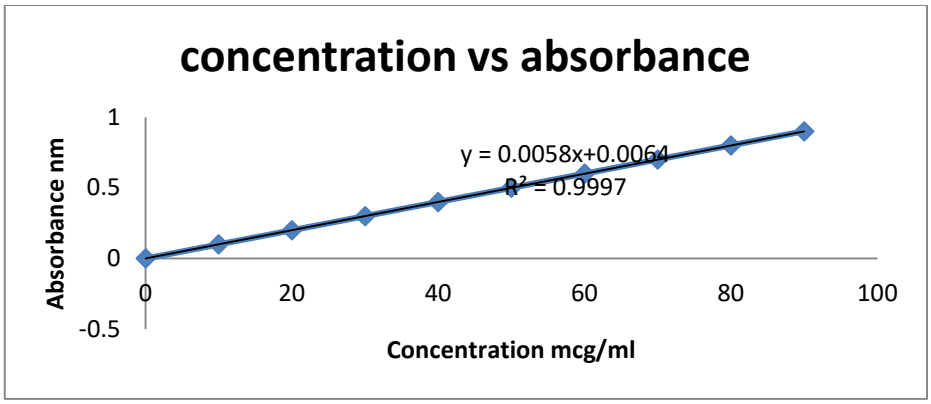
199.66	2436852
249.57	3071035
299.49	3626465



Standard curve for acetaminophen is observed in 5.8PH phosphate buffer. It is evident that linearity is observed in this media.

Standard graph of Methocarbamol:

concentration	Absorbance
0	0
10	0.063
20	0.133
30	0.194
40	0.240
50	0.292
60	0.362
70	0.421
80	0.470
90	0.532
100	0.603



Standard curve for Methocarbamol is observed in Methanol. It is evident that linearity is observed in this media.

COMPARATIVE DATA OF VARIOUS FORMULATIONS:

METHOCARBAMOL LAYER:

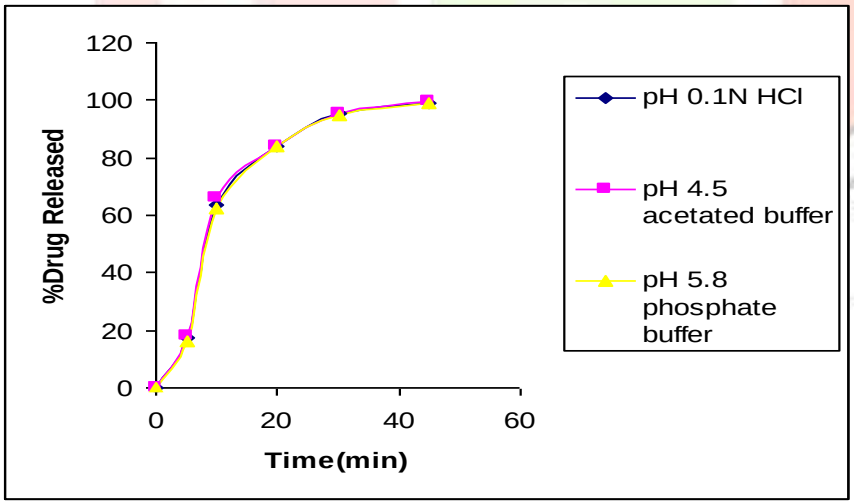
Trial / Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
	% COMPOSITION									
Methocarbamol	76.63	76.63	76.63	76.63	76.63	76.63	83.0	83.0	83.0	83.0
Pregelatinised starch	5.90	4.35	4.35	4.30	4.30	4.30	4.30	4.20	4.20	4.20
Microcrystalline cellulose	10.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Binder										
PVPK-90(F1)/30	1.0	0.8	0.3	0.3	0.3	0.3	0.30	0.30	0.30	0.30
D&C Yellow#10	-	-	-	0.05	0.01	0.01	0.01	0.01	0.009	0.008
FD&C blue#1	-	-	-	-	0.00275	0.00375	0.0037	0.0037	0.0034	0.0031
Sodium lauryl sulphate	-	-	-	-	-	-	-	0.10	0.10	0.10
Lubrication										
Sodium starch glycolate	0.55	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Microcrystalline cellulose	5.0	9.5	10.0	10.0	10.0	10.0	3.68	3.68	3.68	3.68
Magnesium stearate	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60
Colloidal silicon dioxide	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
TOTAL	100									

RMG - Rapid Mixer Granulator

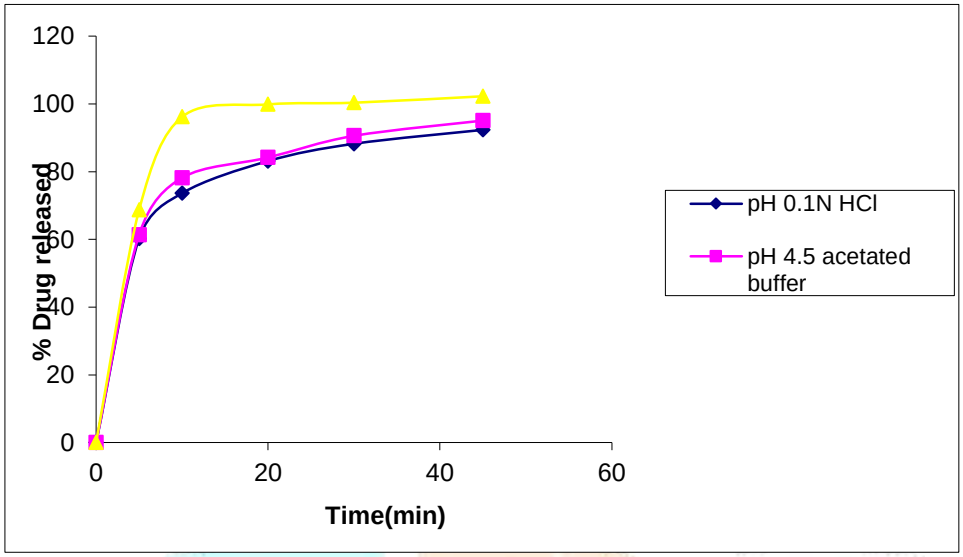
- FBP – Fluid Bed Processor
- RMG - Rapid Mixer Granulator

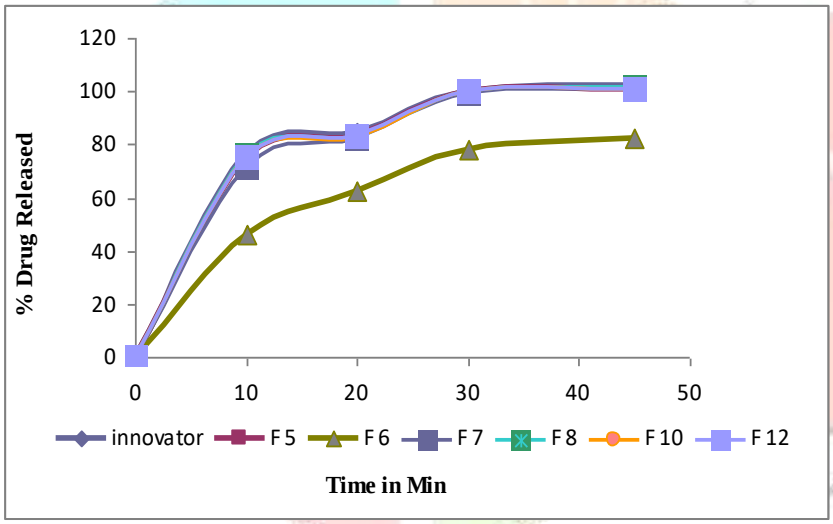
ACETAMINOPHEN LAYER

Trial / Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
	% COMPOSITION									
Acetaminophen	90	90	90	90	90	90	90	90	90	90
Pregelatinized starch	7.06	4.56	3.52	3.1	-	-	-	-	-	-
Binder										
PVP K-30	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Pregelatinized starch	-	2.5	3.5	3.92	7.02	7.02	7.02	7.02	7.02	7.02
Lubrication										
Sodium starch glycolate	1.78	1.78	1.78	1.78	1.78	1.78	1.78	1.78	1.78	1.78
Stearic acid	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
TOTAL	100									
PROCESS	RMG	FBP	FBP	FBP	FBP	RMG	FBP	FBP	FBP	FBP

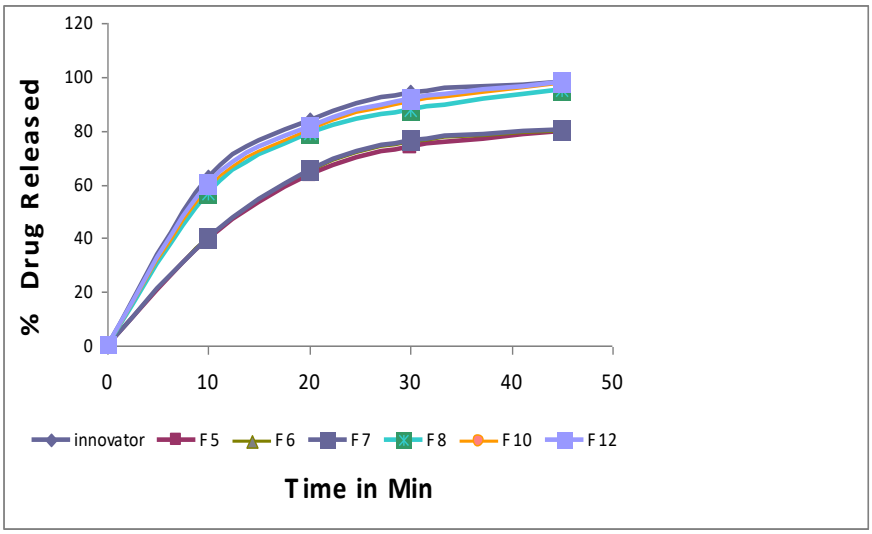


Graphical representation of Comparative In-Vitro dissolution study of Methocarbamol layer of marketed product in different media





Graphical representation of Comparative In-Vitro dissolution study of Acetaminophen layer of Marketed product and different formulation in pH 5.8 phosphate buffer media.



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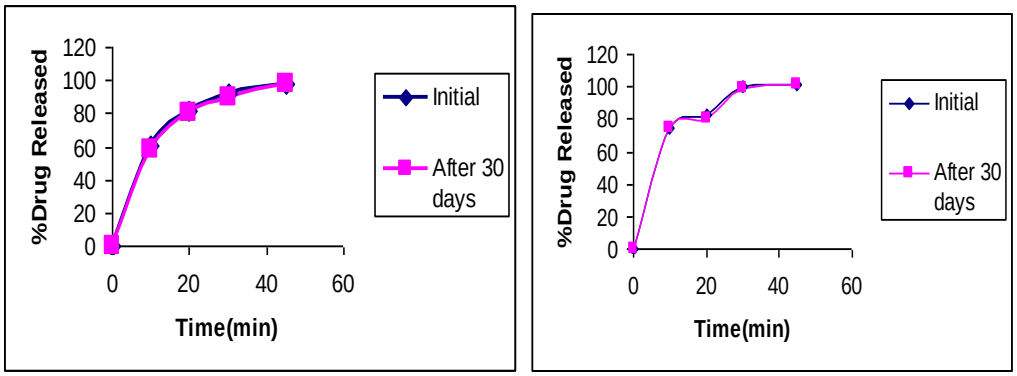
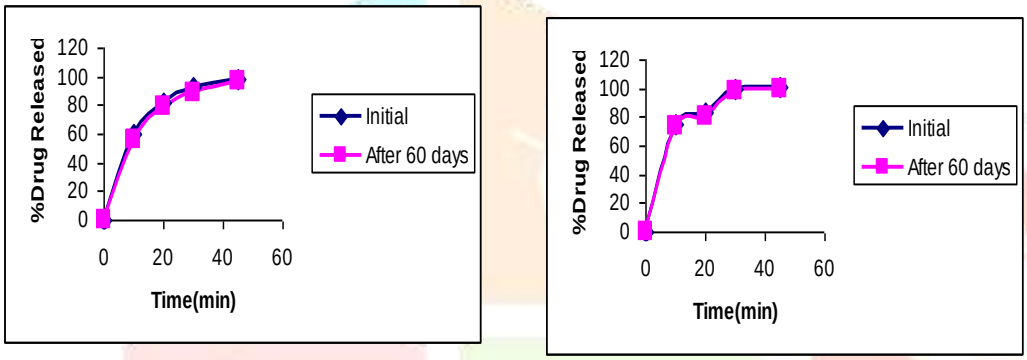
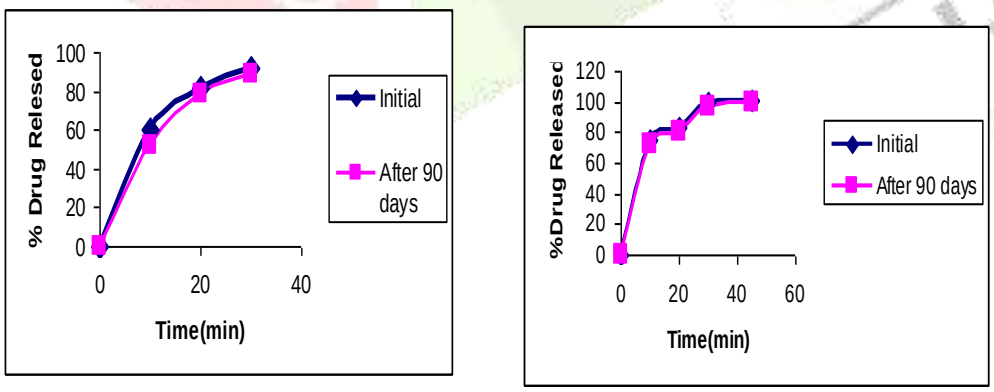


Graphical representation of In- Vitro Drug release profile of Methocarbamol and Acetaminophen Bilayered Tablets stability charging after 30 days Results



Graphical representation of In- Vitro Drug release profile of Methocarbamol and Acetaminophen Bilayered tablets stability charging after 60 days Results



Graphical representation of In- Vitro Drug release profile of Methocarbamol and Acetaminophen Bilayered tablets stability charging after 90 days Results

Discussions: All 3 months stability data of Methocarbamol and Acetaminophen Bilayered Tablets were found to satisfactory

SUMMARY AND CONCLUSION

The study was undertaken with an aim to formulate combination of pain reliefing agents as bilayer tablets. The literature shows that Methocarbamol is a skeletal muscle relaxant which acting centrally through inhibiting inter neuronal activity and blocking polysynaptic reflex pathway at spinal cord and at descending reticular formation at brain. Due to this reason it is used mainly in the treatment of chronic low back pain. Acetaminophen is thought to act primarily in the CNS, increasing the pain threshold by inhibiting both isoforms of cyclooxygenase, COX-1 and COX-2, enzymes involved in prostaglandin (PG) synthesis, which is responsible for pain sensation.

At the present efforts are directed towards the formulation development of bilayer dosage form for the pain reliefing drugs. During the phase of investigation various factor likely to affect the performance of the bilayer apparatus are felt necessary to be discussed in light of sound theoretical knowledge. Dissolution rate, intrinsic solubility, particle size of the drug, hardness, thickness, friability found to be critical during granulation are some of the factors found to be critical during the development based on the experimental findings.

In the present study, SLS was found to play a great role in enhancing the dissolution of the Methocarbamol layer.

In the study high percentage of drugs in the granulation were cost effective and as well as cause of requiring less compression force which is very important for the bi layer technology.

With the data from literature review, Preformulation study prototype formulation was started, placing Acetaminophen layer on precompressed Methocarbamol blend optimized layer. For both layer wet granulation process was used for the formulation, where Methocarbamol layer in RMG process and Acetaminophen layer in FBP process.

Granules were evaluated for test such as LOD, Bulk density, Tapped density, Compressibility index, Hausner ratio and sieve analysis before being punched as a tablet. The prepared tablets were then tested for weight variation, thickness, hardness and friability. In-vitro dissolution tests were performed and F10 values were calculated. Dissolution profile was found to match with the Innovator product and F10 value was found to be satisfactory.

From the above study results, it can be conclude that F10 formulation showed the desire results and was found to be suitable for large scale production. Two reproducible batch were done, process parameter and results were found similar with the optimized formulation.

The stability study of the final formulation for 3 months shows that the formulation is stable enough at 25 ºC/ 60%RH and 40^0C/75%RH .

Accordingly, it can be concluded that the final formulation is a robust one and the performance is less likely to effected by the various factors study. An excellent in vitro-in vivo correlation is expected as evidence from degree of similarity found in dissolution study.

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