FORMULATION AND EVALUATION OF BILAYERED TABLETS OF ACETAMINOPHEN AND METHOCARBAMOL

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In partial fulfillment

For the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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APRIL 2012

DECLARATION BY CANDIDATE

It gives me great pleasure and satisfaction to declare that the dissertation entitled **"FORMULATION AND EVALUATION OF BILAYERED TABLETS OF ACETAMINOPHEN AND METHOCARBAMOL"** *is a bonafide genuine research work carried out by me in our college and in the Production-Formulation department of* ***Granules India Pvt Ltd,*** *Ranga Reddy Dist, under the guidance,* ***of Mr.T.Akelesh****, Asst. Professor,* ***Dept. of Pharmaceutics, R.V.S College of Pharmaceutical Sciences,*** *Sulur, Coimbatore and* ***Mr. M.S Vijay Kumar****, Deputy Manager, Production-Formulation department of* ***Granules India Pvt Ltd,*** *Ranga Reddy Dist.*

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TO WHOM SO EVER IT MAY CONCERN

This is to certify that Mr.Sreenivasa Reddy.Y, S/o. Bhaskara Reddy.Y, a student of M.Pharmacy, R.V.S College of Pharmacy, M.G.R University, Sulur, Coimbatore, Tamilnadu has undergone Project work in Production - Formulations department of our organization at our Gagillapur facility during the period from 3rd August, 2011 to 2nd February, 2012. His project title is **"FORMULATION AND EVALUATION OF BILAYERED TABLETS OF ACETAMINOPHEN AND METHOCARBAMOL".**

During the tenure of training we found his sincere.

We wish him all success in his future endeavors.

For **GRANULES INDIA LIMITED**

B.Prabhakar Reddy
Manager – HR & Admn.

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SREENIVAASA REDDY.

LIST OF ABBREVIATIONS

S.No	Abbreviation used	Meaning
1	NSAIDS	Non-steroidal anti inflammatory drugs
2	COX	Cyclooxygenase
3	APAP	Acetaminophen
4	ICH	International conference on harmonization
5	RP-HPLC	Reverse phase-high performance liquid chromatography
6	API	Active pharmaceutical ingredient
7	P^H	Hydrogen ion concentration
8	SR	Sustained release
9	PVP	Polyvinyl pyrolidone
10	PGE	Prostaglandin E
11	BCS	Bio pharmaceutical classification standards
12	LOD	Loss on drying
13	NLT	Not less than
14	NMT	Not more than
15	BD	Bulk density
16	TD	Tapped density
17	CI	Compressibility index
18	HR	Hausner's ratio
19	CNS	Central nervous system
20	^OC	Degree centi grade
21	L	Litres
22	GIT	Gastrointestinal tract
23	Mg	Milligrams
24	Rpm	Rounds per minute
25	Mm	Millimeter
26	Kg	Kilo gram
27	RH	Relative humidity
28	%	Percentage
29	HPMC	Hydroxy propyl methyl cellulose
30	PVDF	Polyvinylidene fluoride

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Abstract:

The basic aim of any Bi-layer tablet formulation is to separate physically or chemically incompatible ingredients and to produce repeat action or prolonged action tablet. The present study was aimed at developing a bilayer tablet of Acetaminophen and Methocarbamol. Acetaminophen is used as an Analgesic, Non-Narcotic, antipyretic, Methocarbamol is used as an Anti-inflammatory, skeletal muscle relaxant. Totally 9 formulations are prepared with Acetaminophen and Methocarbamol granules prepared separately in a rapid mixer granulator. Pre compression parameters like Bulk density, True density, Angle of repose indicate all the formulations are showing good flow properties. Tablets are compressed using SEJONG bilayer compression machine and tablets are evaluated for post compression parameters Weight variation, Hardness, Friability, Disintegration and Dissolution parameters. Among all the formulations F8 is showing the release profile similar to the Innovator. The compressed bilayer tablets was packed in blisters and subjected to stability studies at 40°C and 75% RH, 25°C and 60% RH. Samples were analyzed at regular intervals as mentioned in stability protocol. From the study, it may be concluded that bilayer tablet of Acetaminophen and Methocarbamol can be prepared as immediate release formulation compared to conventional formulations.

1. INTRODUCTION

1.1 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS[1,2,3,4,5,6,26]

Prostaglandins are a family of chemicals that are produced by the cells of the body and have several important functions. They promote inflammation, pain, and fever; support the blood clotting function of platelets; and protect the lining of the stomach from the damaging effects of acid.

Prostaglandins are produced within the body cells by the enzyme cyclooxygenase (COX). There are two COX enzymes, COX-1 and COX-2. Both enzymes produce prostaglandins that promote inflammation, pain, and fever. However, only COX-1 produces prostaglandins that support platelets. Non steroidal anti-inflammatory drugs (NSAIDs) block the COX enzymes and reduce prostaglandins throughout the body. As a consequence, ongoing inflammation, pain, and fever are reduced. Since the prostaglandins that protect the stomach and support platelets and blood clotting also are reduced, NSAIDs can cause ulcers in the stomach and promote bleeding.

NSAIDs vary in their potency, duration of action, how they are eliminated from the body, how strongly they inhibit COX-1 and their tendency to cause ulcers and promote bleeding. The more an NSAID blocks COX-1, the greater is its tendency to cause ulcers and promote bleeding. One NSAID, celecoxib(Celebrex), blocks COX-2 but has little effect on COX-1, and is therefore further classified as a selective COX-2 inhibitor.

Aspirin is a unique NSAID, not only because of its many uses, but because it is the only NSAID that inhibits the clotting of blood for a prolonged period (4 to 7 days). Most NSAIDs inhibit the clotting of blood for only a few hours. Ketorolac (Toradol) is a very potent NSAID and is used for moderately severe acute pain that usually requires narcotics. Ketorolac causes ulcers more frequently than other NSAID. Therefore, it is not used for more than five days.

1.2 CLASSIFICATION[7,8,9,10,11]

NSAIDs can be classified based on their chemical structure or mechanism of action. Older NSAIDs were known long before their mechanism of action was elucidated and were for this reason classified by chemical structure or origin.

Salicylates

- Aspirin (acetylsalicylic acid)
- Diflunisal
- Salsalate

p-amino phenol derivatives

- Paracetamol
- phenacetin

Propionic acid derivatives

- Ibuprofen
- Naproxen
- Fenoprofen
- Ketoprofen
- Flurbiprofen
- Oxaprozin
- Loxoprofen

Acetic acid derivatives

- Indomethacin
- Sulindac
- Etodolac

- Ketorolac
- Diclofenac
- Nabumetone
- Piroxicam
- Meloxicam
- Tenoxicam
- Droxicam
- Lornoxicam
- Isoxicam

Fenamic acid derivatives (Fenamates)

- Mefenamic acid
- Meclofenamic acid
- Flufenamic acid
- Tolfenamic acid

Selective COX-2 inhibitors (Coxibs)

- Celecoxib
- Rofecoxib
- Valdecoxib
- Parecoxib
- Lumiracoxib
- Etoricoxib

Sulphonanilides

- Nimesulide

Others

- Licofelone

1.3 ACETAMINOPHEN[12,13,14,22,23]

Acetaminophen (Paracetamol, APAP), is an over the counter pain reliever that also reduces fever. It is commonly used to reduce pain associated with headaches, migraines, back ache, cold, and flu. Its general mechanism of action is inhibition of the COX-2 enzyme. Acetaminophen belongs to a class of drugs called analgesics (pain relievers) and antipyretics (fever reducers). The exact mechanism of action of acetaminophen is not known. Acetaminophen relieves pain by elevating the pain threshold, that is, by requiring a greater amount of pain to develop before a person feels.

Analgesics[15,16,17,18,28]

Acetaminophen is used to provide temporary analgesia in the treatment of mild to moderate pain. The drug is most effective in relieving low intensity pain of non-visceral origin. Acetaminophen does not have antirheumatic effects. Unlike salicylates and prototypical non-steroidal anti-inflammatory agents (NSAIAs), acetaminophen does not usually depress prothrombin levels. In addition, acetaminophen produces a lower incidence of gastric irritation, erosion, or bleeding than do salicylates. Acetaminophen has been used in the treatment of pain in various combinations with aspirin, caffeine, opiates, and/or other agents. Acetaminophen (650-mg oral doses) in combination with oral doses of an opiate (e.g., codeine, oxycodone) produces greater analgesic effect than that produced by either acetaminophen or higher doses of the opiate alone. In addition, there is little evidence that such combinations cause fewer adverse effects than higher doses of the individual agents alone.

Antipyretics[19,20,21]

Acetaminophen is used frequently to lower body temperature in febrile patients in whom fever may be deleterious or in whom considerable relief is obtained when fever is lowered.

However, antipyretic therapy is generally nonspecific, does not influence the course of the underlying disease, and may obscure the patient's illness. Parents and caregivers of paediatric patients should be reassured that while some parental anxiety. Over fever is understandable, the principal reason for treating fever is for patient. Comfort and that complete normalization of body temperature is not necessary and may not be possible. To minimize the risk of acetaminophen over dosage, alternative antipyretics should be considered for children at increased risk of developing toxicity and in those with refractory fever.

1.4 METHOCARBAMOL[29]

Methocarbamol is a central muscle relaxant for skeletal muscles, used to treat spasms. It is structurally related to guaifenesin. Methocarbamol's exact mechanism of causing skeletal muscle relaxation is unknown. It is thought to work centrally, perhaps by general depressant effects. It has no direct relaxant effects on striated muscle, nerve fibers, or the motor endplate. It will not directly relax contracted skeletal muscles. The drug has a secondary sedative effect.

SKELETAL MUSCLE SPASMOLYTICS[29]

Muscle spasticity is a characteristic of many clinical conditions, including trauma, myositis, muscular and ligamentous sprains and strains, intervertebral disk disease, tetanus, strychnine poisoning, neurologic disorders, and exertional rhabdomyolysis. An increase in tonic stretch reflexes originates from the CNS with involvement of descending pathways and results in hyper excitability of motor neurons in the spinal cord. Drug therapy alleviates muscle spasms by modifying the stretch reflex arc or by interfering with the excitation-coupling process in the muscle itself. Centrally acting muscle relaxants block interneuronal pathways in the spinal cord and in the midbrain reticular activating system. Some drugs also have sedative effects, which are beneficial to anxious, painful animals. The hydantoin derivatives have a direct action on muscle.

Methocarbamol is a centrally acting muscle relaxant chemically related to guaifenesin. Its exact mechanism of action is unknown, and it has no direct relaxant effect on striated muscle, nerve fibers, or the motor endplate. It also has a sedative effect. In dogs, cats, and horses, methocarbamol is indicated as adjunct therapy of acute inflammatory and traumatic conditions of skeletal muscle and to reduce muscle spasms.

Guaifenesin (glyceryl guaiacolate) is a centrally acting muscle relaxant that is believed to depress or block nerve impulse transmission at the internuncial neuron level of the subcortical areas of the brain, brain stem, and spinal cord. It also has mild analgesic and sedative actions. Guaifenesin is given IV to induce muscle relaxation as an adjunct to anesthesia for short procedures. It relaxes both laryngeal and pharyngeal muscles, allowing easier intubation, but has little effect on diaphragm and respiratory function. It may cause transient increases in cardiac rate and decreases in blood pressure.

1.5 TABLETS[30,31,32]

Tablets are solid unit dosage form, flat or biconvex in shape, prepared by may be swallowed whole or being chewed. Some are dissolved or dispersed in water before administration. Implants or passeries may also be presented in the form of tablet. Tablet may vary in shape and differ greatly in size and weight depending on the amount of medicinal substance and the intended mode of administration.

1.5.1 Advantages of tablet

- Large scale manufacturing is feasible in comparison to other dosage forms. Therefore, economy can be achieved.
- Accuracy of dose is maintained since tablet is a solid unit dosage form.
- Longer expiry period and minimum microbial spillage owing to lower moisture content.
- As tablet is not a sterile dosage form, stringent environmental conditions are not required in the tablet department.
- Ease of packaging (blister or strip) and easy handling over liquid dosage form.
- Easy to transport in bulk. Emergency supplies can be carried by patients.
- Organoleptic properties (taste, appearance and odour) are best improved by coating of tablet.

- Product identification is easy and markings done with the help of grooved punches and printing with edible ink.

- Different types of tablets are available like buccal, floating, colon targeting, effervescent, dispersible, soluble, and chewable, etc.

- In comparison to parenterals dosage form, a doctor or a nurse is not required for administration. I.e. self-administration is possible.

- In comparison to capsules, tablets are more tamperproof.

1.5.2 Disadvantages of tablet

- It is difficult to convert a high dose poorly compressible API into a tablet of suitable size for human use.

- Difficult to formulate a drug with poor wettability, slow dissolution into a tablet.

- Slow onset of action as compared to parenterals, liquid orals and capsules.

- The amount of liquid drug (e.g. Vitamin E, Simethicone) that can be trapped into a tablet is very less.

- Difficult to swallow for kids, terminally ill and geriatric patients.

- Patients undergoing radiotherapy cannot swallow tablet.

1.6 TYPES OF TABLETS[31,32,33]

With advancement in technology and increase in awareness towards modification in standard tablet to achieve better bioavailability, newer and more efficient tablet dosage forms are being developed.

To understand each dosage form, tablets here are classified by their route of administration.

A) Oral tablets for ingestion

These tablets are meant to be swallowed intact along with a sufficient quantity of potable water. Exception is chewable tablet. Over 90% of the tablets manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction.

B) Multiple compressed tablets

- Compression coated tablet
- Layered tablet
- Delayed action tablet
- Floating tablet
- Colon targeting tablet
- Chewable tablet
- Dispersible tablet
-

C) Tablets used in the oral cavity

The tablets under this group are aimed release API in oral cavity or to provide local action in this region. The tablets under this category avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action.

- Lozenges and troches
- Buccal tablet Dental cones
- Mouth dissolved tablet

D) Tablets administered by other routes

These tablets are administered by other route except for the oral cavity and so the drugs are avoided from passing through gastro intestinal tract. These tablets may be inserted into other body cavities or directly placed below the skin to be absorbed into systemic circulation from the site of application.

- Vaginal tablet,
- Implants

E) Tablets used to prepare solution

The tablets under this category are required to be dissolved first in water or other solvents before administration or application. This solution may be for ingestion or parenteral application or for topical use depending upon type of medicament used

- Effervescent tablet
- Hypodermic tablet

1.7 FORMULATION OF TABLET[31,32,33,34,35]

Tablet generally consists of mixture of active pharmaceutical ingredient and excipient. Excipient means any component other than the active pharmaceutical ingredient(s). While selecting excipients for any formulation following things should be considered wherever possible.

- Keep the excipients to a minimum in number
- Minimize the quantity of each excipients
- Multifunctional excipients may be given preference over unifunctional excipients.

1.7.1 Excipients are chosen in tablet formulation to perform a variety of functions like

- For providing essential manufacturing technology functions (binders, glidants, lubricants may be added)
- For enhancing patient acceptance (flavors, colorants may be added)
- For providing aid in product identification (colorants may be added)
- For Optimizing or modifying drug release (disintegrants, hydrophilic polymers, wetting agents, biodegradable polymers may be added)
- For enhancing stability (antioxidant, UV absorbers may be added)

1.8) ROLE OF EXCIPIENTS IN SOLID DOSAGE FORM[36]

A) Diluents or Fillers

Diluents are added where the quantity of active ingredients is small or difficult to compress. Eg: lactose, mannitol.

B) Binders or Granulating agents or Adhesive

Binders help powders fuse or link particles to another. Eg: starch, povidone.

C) Disintegrants

Disintegrants help the tablet break up after the patients ingest it. Eg: cross carmellose sodium, starch.

D) Lubricants

Lubricants prevent powders from sticking to the metal component of the tablet press and tablet press tooling. Eg: talc, aerosol.

E) Glidant

Glidants are agents that are added to the tablet formulation in order to improve the flow property of the granulation. They act by reducing inter particulate friction. Eg: Magnesium Stearate.

F) Adsorbents

Adsorbents are the substances included in a formulation that are capable of holding quantities of fluid in an apparently dry state. Oil soluble drugs, fluid extracts or oil can be mixed with adsorbents and then granulated and compressed into the tablets. Eg: fumed silica, microcrystalline cellulose, magnesium carbonate.

G) Colorants

Colorants are often added to tablet formulation to add value or for product identification.

1.9) TABLET MANUFACTURING PROCESS[31,32,33,39]

A tablet with good characterization is made in the granulation process. Joined particles within a given granulation process will improve flow and compression characteristics, reduce segregation, improve content uniformity, and eliminate excessive amount of fine particles. The results improve yield, reduced tablet defects, increased productivity and reduced down time. The objective of the process is to combine ingredients to produce a quality tablet.

Table No: 1 Steps Involved in Tablet Manufacturing Process

S.NO	PROCESSING STEPS	DIRECT COMPRESSION	WET GRANULATION	DRY GRANULATION
1	RAW MATERIALS	YES	YES	YES
2	WEIGHING	YES	YES	YES
3	SCREENING	YES	YES	YES
4	MIXING	YES	YES	YES
5	COMPRES	YES	NO	YES
6	WET MASS	NO	YES	NO
7	MILLING	NO	NO	YES
8	DRYING	NO	YES	NO
9	SHIFTING	NO	YES	YES
10	MIXING	NO	YES	YES
11	COMPRESSION	NO	YES	YES

1.10) IMMEDIATE RELEASE TABLETS[37,38]

Tablets can be designed for use as immediate release products or by suitable modifications of the composition and manufacturing process can also be designed as modified release products with many different potential release patterns.

However for immediate release tablets, tablet disintegrants play an important role in ensuring that the tablet matrix break up on contact with the fluid in the stomach to allow the release of the active drug which then become available in whole or in part, for absorption from the gastrointestinal tract (GIT). Although most drugs are absorbed from the GIT after passing through the stomach, it is never the less important with immediate release products that the tablets disintegrates properly in the stomach to release the drug and allow it to be absorbed quickly after passing through the pyloric sphincter and on into duodenum and beyond.

1.11) BILAYERED TABLETS[40,43]

Dual release is a unit compressed tablet dosage form intended for oral application. It contains two parts, in which one part is having conventional or immediate release part while the other is sustained or controlled released part. In this chemically incompatible materials or those which separate in a mixed granulation present in the same tablet. For sustained action of products each layer may be formulated for different release characteristics. Sometimes different drug formulated in a same tablet to achieve different pharmacological action from a single tablet.

APPLICATIONS:

a) Used in the combination therapy and to deliver the loading dose a sustained dose of the same or different drugs.

b) Used for bilayer floating tablet in which one layer is floating layer and another one is releases layer of the drug and to deliver tow different drugs having different releases profiles.

ADVANTAGES:

a) Better product compliance, therapeutic efficacy and provide good efficiency.

b) Red/uced dosing intervals, number of dosing and number dosage forms.

c) Incompatible drugs are given by separating these drugs by inert materials.

1.12) STABILITY STUDIES AS PER ICH GUIDELINES[41,44]

Stability is defined as the capacity of a drug substance of a drug product to remain within the established specifications to maintain its identity, strength, quality and purity throughout the retest or expiration dating period.

The objectives of stability of stability studies determine the shelf life, namely the time period of storage at a specific condition within which the drug product still meets its established specifications.

Stability is essential factor of quality, safety and efficacy of a drug product. A drug product, which is not of sufficient stability results in changes in physical (like hardness, dissolution rate, phase separation etc) as well as chemical characteristics (formulation of high risk decomposition substances).

The chemical stability of drug is of great importance since it becomes less effective as it undergoes degradation. Also drug decomposition may yield toxic byproducts that are harmful to patients. Microbiological instability of a sterile drug product could also be hazardous.

Stability valuation of drug substance is the key to drug quality as it determines the efficacy of any drug or dosage forms. Stability assessment of drug products and drug substances are mandated by regulatory agencies across the world.

In fact stability testing issues are responsible for a number of audit findings by regulatory agencies. Stability testing problems are regularly cited in warning letters and sometimes results in costly product recall.

Stability testing provides evidence that the quality of drug substance change with time under the influence of various environmental conditions such as temperature, relative humidity etc.

Stability studies consist of a series of test in order to maintain an assurance of stability of drug product, namely maintenance of the drug product packed in specified packaging material and stored in established storage condition within the determined time period

- **AIM OF STUDY:**

Developing a new formula for bilayer tablet containing Acetaminophen and Methocarbamol, by Evaluation of trial products and Drug release profile. Stability testing alsoshould be done as per ICH guidelines.

- **OBJECTIVE OF STUDY:**

  - To carry out literature survey of the drug molecules.
  - Formulation of the tablets using different trials
  - To analyse the trial samples.
  - To optimize the final formula.

3. PLAN OF WORK

- Development of final formula.

- Literature collection of trial product.
- Pre formulation studies.
- Formulation of trial products.
- Dissolution studies of trials.
- Finalization of quantitative formula.

4. REVIEW OF LITERATURE:

- ***Remya P.N, Damodharan N, Sulakshan Kumar C.V et al (2010).,***[45] To develop a robust formulation of Bi-layer tablets of Ibuprofen and Methocarbamol using Povidone k-30 as

binder. The basic aim of any Bi-layer tablet formulation is to separate physically or chemically incompatible ingredients and to produce repeat action or prolonged action tablet. The drug products may be developed to reduce Low back pain. The mechanism of Methocarbamol is a skeletal muscle relaxant which acting centrally through inhibiting inter neuronal activity and blocking polysynaptic reflex pathway at spinal card. Ibuprofen is a pain relieving agent which inhibits the activity of Cyclooxygenase an enzyme crucial for synthesis of prostaglandins. A total number of nine formulations have been taken to optimize and develop a robust and stable formulation. Among the formulations tablets of formulation F8 containing Ibuprofen 200mg and Methocarbamol 500mg per tablet was taken as optimized formula due to its higher rate of dissolution 95.1 to 97.2% was measure by taking absorbance by HPLC technique.

- ***Mallikarjuna Reddy, N. K. Durga Devi*, B. R. Madhavi et al (2010).,***[46] simultaneous determination of Acetaminophen and Methocarbamol in bilayered tablet dosage form formulated by RP-HPLC. A Develosil ODS-MG-5 column having 100×4.6mm internal dimensions was used as stationary phase and Milli Q water, Methanol & Glacial acetic acid in the ratio of 600:400:15 as mobile phase. The flow rate was 1.0ml/min & effluent monitored at 273nm.The retention times of Acetaminophen & Methocarbamol were found to be 1.846 and 4.713 min. respectively The linearity range for acetaminophen and methocarbamol was 75-600 and 50-400 µg/ml with correlation values of 0.9998 and 0.999 respectively. The recovery was found to be in the range of 98.28-99.96% for acetaminophen and 99.36-101.64% for methocarbamol.

- ***Deelip Derle*, Omkar Joshi, Ashish Pawar et al (2009).,***[47] The purpose of the study was to formulate and evaluate mucoadhesive bi-layer buccal tablets of propranolol hydrochloride tablets using the bioadhesive polymers such as sodium alginate and carbopol 971 P along with ethyl cellulose as an impermeable backing layer. The dose in the formulation for fast release was 25 mg, the maintenance dose or sustained dose (55 mg) of propranolol hydrochloride. Tablets containing sodium alginate and carbopol 971 P in the ratio of 5:1 showed the maximum percentage of *in vitro* drug release without disintegration in 12 hoursby UV Double beam spectrophotometer at 290 nm.. The swelling index was proportional to sodium alginate content and inversely proportional to carbopol 971 P content. The surface pH of all tablets was found to be satisfactory, closeto

neutral pH; hence, no irritation would observe with these tablets. The mechanism of drug release was found to be zero-order kinetics.

- ***N.N.Rajendran*, R.Natarajan, R. Subashini et al (2011).,***[48] The present study was to establish and evaluate the Bi-layer tablets containing Metformin HCl as sustained release and Pioglitazone HCl as immediate release layer. Sustained layer were prepared by wet granulation method using different viscosity grade of HPMC (HPMC K4M & HPMC K100M) as polymers and immediate release layer were prepared by direct compression method using superdisintegrants such as sodium starch glycolate and crosscarmellose sodium. The result showed that combinations of polymers namely HPMC K100M and HPMC K4M in sustained layer can control the release of drug. The *in vitro* release profiles of drug from sustained release layer could be best expressed by Higuchi's equation as the plots showed high linearity (R2 >0.988) and diffusion was the dominant mechanism of drug release. The formulations (P6M7) having immediate release layer produces immediate effect within 54 second followed by sustained release (97.35%) at 8 hrs and it comparable with innovator.
- ***S.Jayaprakash, S. Mohamed Halith, K.Kulathuran Pilla et al (2011).,***[49] Bilayer tablets of Amlodipine besilate (IR) Metoprolol succinate (SR) were formulated and evaluated for the management of hypertension. In the formulation of immediate release sodium starch glycolate and pregelatinised starch were used as super disintegrant and was directly compressed. For It was found that the optimized formulation showed 90.46% release for Metoprolol succinate in 20 hours respectively.However, Amlodipine besilate released 98.28% at the end of 30 minutes.The IR spectrum and DSC studies revealed that there is no disturbance in the principal peaks of pure drugs Metoprolol succinate and Amlodipine besilate. The kinetic studies of the formulations revealed that diffusion is the predominant mechanism of drug and release follows first order kinetics.
- ***Md. Saleem et al (2011).,***[50] has done the validation for ibuprofen 200mg & methocarbamol 500mg caplet dosage form. Critical parameters involved in sifting,

drymixing, preparation of granulating agent, wet mixing, wet milling, drying, sizing, lubrication, compression stages & coating were identified and evaluated.

- ***Dhaneshwar shep et.al (2010).,***[51] studied the bioequivalence and pharmacokinetic evaluation of two formulations of paracetamol ER 650mg accesing the pharmacokinetic parameters C_{max}, T_{max},$T_{1/2}$, AUC_{0-t}, $AUC_{0-\infty}$ and K_{el} and compared the bioequivalence range and is found to be within the range 80% to 125%.
- ***Venkatesh radhakrishnan et.al (2011).,***[52] has studied the dissolution profile of bilayered conventional release paracetamol and sustained release diclofenac sodium, for simultaneous UV method determination and compared with the market product and they are fitted to higuchi model.
- ***Kiran muscle et.al (2011).,***[53] has donethe formulation and development of bilayered tablet of diclofenac as sustained release form using polyethylene glycol, microcrystalline cellulose and crospovidone as independent variables for fabricating paracetamol tablets diclofenac tablets prepared using HPMC as matrixing agent.
- ***Hosna Banu et.al (2011)***[54] has done the formulation development of bilayered acetaminophen tablets for extended release of drug with other being immediate release layer tablets are prepared by wet granulation method using HPMC 15cps, HPMC 100cps, K4MCR as release rate retardants and analyzer for zero order, first order Higuchi, Kosmeyer, Peppas models for the release kinetics.
- ***MA Naeem et.al (2010)***[55] has formulated and evaluated controlled release bilayer tablets containing micro encapsulated tramadol & acetaminophen. Micro particles are prepared with Ec by coacervation by temperature change method and micro particles are compressed in to bilayered tablets and evaluated by FTIR, XRD, DSC, TGA and drug release kinetic studies.

5. DRUG AND EXCIPIENTS PROFILE:

5.1 DRUG PROFILE:

5.1.1 ACETAMINOPHEN DRUG PROFILE[12,13,14]

Figure No: 1 Structural Formula

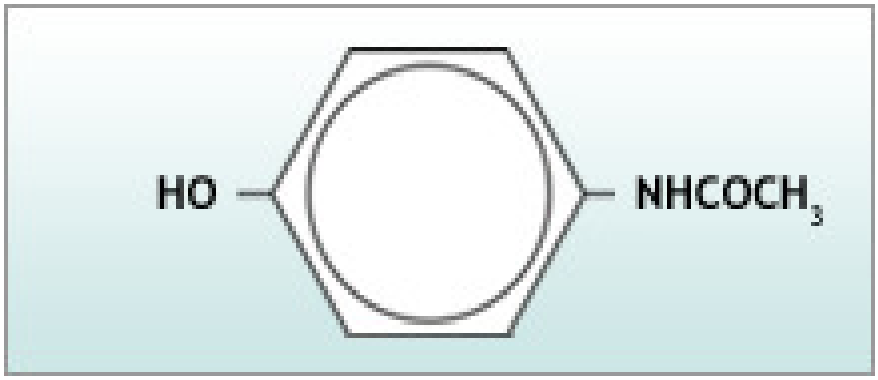


Table No: 2 Acetaminophen Drug Profile

Properties	**Information**
Molecular Formula	$C_8H_9NO_2$
Molecular weight	151.16
IUPAC name	N-(4-hydroxyphenyl)acetamide
Macroscopic Appearance	White, crystalline powder
Half-life	1 to 4 hours
Solubility	Slightly soluble in Water, Soluble in Organic solvents.
P^H	Stable at a pH between 4 and 7 at 25°C.
P^{ka}	9.51 at 25°C.
Use	Analgesics, Non-Narcotic, antipyretics

Mechanism of Action

Analgesia[15,16,17,18,24]

Although the exact site and mechanism of analgesic action is not clearly defined, acetaminophen appears to produce analgesia by elevation of the pain threshold. The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate and substance P.

Antipyretic[19,20,21,25,27]

Investigations indicate that endogenous pyrogens produced by leukocytes cause an elevation of prostaglandin E (PGE) in the cerebrospinal fluid. Fever results when the elevated PGE acts on the pre optic area of the anterior hypothalamus to decrease heat loss and increase heat gain. Acetaminophen has been shown to inhibit the action of endogenous pyrogens on the heat-regulating centers in the brain by blocking the formation and release of prostaglandins in the central nervous system. Inhibition of arachidonic acid metabolism is not requisite for the antipyretic effect of acetaminophen. Acetaminophen does not depend upon the activation of the arginine vasopressin V-1 receptor to induce antipyresis as has been noted in rats treated with indomethacin and salicylates. This has been demonstrated in animals by observing a decrease in both fever and PGE activity following administration of acetaminophen to unanesthetized cats, and in rabbits and dogs when brain prostaglandin synthetase was inhibited by the administration of acetaminophen.

5.1.2 METHOCARBAMOL DRUG PROFILE [29]

Figure No: 2 Structural Formula of Methocarbamol

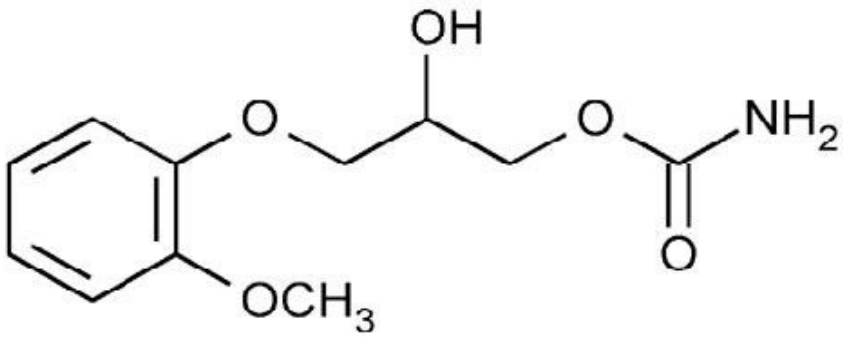


Table No: 3 Methocarbamol Drug Profile

Properties	**Information**
Molecular Formula	$C_{11}H_{15}NO_5$
Molecular weight	241.24
IUPAC name	3-(2-methoxyphenoxy)-1,2-propanediol 1-carbamate.
Macroscopic Appearance	White, crystalline powder.
Half-life	1-2 hours
Solubility	Sparingly soluble in Water
P^H	Stable at a pH between 4 and 7 at 25°C.
P^{ka}	9.51 at 25°C.
Use	Anti-inflammatory, skeletal muscle relaxant

Mechanism of Action[29]

Methocarbamol is thought to act primarily in the CNS, increasing the pain threshold by inhibiting both isoforms of cyclooxygenase, COX-1, COX-2, and COX-3 enzymes involved in prostaglandin (PG) synthesis. Unlike NSAIDs, Methocarbamol does not inhibit cyclooxygenase in peripheral tissues and, thus, has no peripheral anti-inflammatory affects. While aspirin acts as an irreversible inhibitor of COX and directly blocks the enzyme's active site, studies have found that methocarbamol 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 methocarbamol 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.

5.2 EXCIPIENTS PROFILE

POVIDONE[37,38]

Table No: 4 Povidone excipients Profile

Non-proprietary Names	• BP: Povidone, JP: Povidone, PhEur: Povidonum USP: Povidone
Synonyms	E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer
Empirical formula	$(C_6H_9NO)_n$
Molecular weight	2500–3 000 000
Description	Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.
Functional categories	Disintegrant; dissolution aid; suspending agent; tablet binder.
Solubility	freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water;
Melting point	Softens at 150°C.
Stability and storage	Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the

conditions	powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.
Incompatibilities	It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds.
Applications	Povidone solutions may also be used as coating agents and it is also used as a suspending, stabilizing, or viscosity-increasing agent In tableting, povidone solutions are used as binders in wet-granulation.

MICROCRYSTALLINE CELLULOSE[38]

Table No: 5 Microcrystalline cellulose excipients Profile

Non-proprietary Names	• BP: Microcrystalline cellulose, • PhEur: Cellulosemmicrocristallinum, • JP: Microcrystalline cellulose, • USPNF: Microcrystallinecellulose
Synonyms	Avicel PH; Cellets; Celex; cellulose gel; hellulosummicrocristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.
Empirical formula	$(C_6H_{10}O_5)_n$ where n~220
Molecular weight	3600 g/mol.
Description	MCC occurs as a white, odourless, tasteless, crystalline powder

	composed of porous particle.
Functional categories	Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant
Solubility	Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.
Melting point	260-270°C
Stability and storage conditions	Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place
Incompatibilities	Microcrystalline cellulose is incompatible with strong oxidizing agents
Applications	Microcrystalline cellulose is widely used primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct compression processes. Also as lubricant and disintegrant

MAGNESIUM STEARATE[37]

Table No: 6 Magnesium Stearate excipients Profile

Non-proprietary Names	BP: Magnesium Stearate, JP: Magnesium Stearate ,PhEur: Magnesium Stearate ,

Synonyms	Dibasic magnesium stearate; magnesium distearate; magnesiistearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt; Synpro 90
Empirical formula	$C_{36}H_{70}MgO_4$
Molecular weight	591.24
Description	Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.
Functional Categories	Tablet and capsule lubricant.
Solubility	Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).
Melting point	117–150 °C
Stability and storage conditions	Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials.
Applications	It is primarily used as a lubricant in capsule and tablet manufacture.

STEARIC ACID[38]

Table No: 7 Stearic Acid excipients Profile

	Octadecanoic acid

Non-proprietary Names	
Synonyms	C18:0 (lipid number)
Empirical formula	C18H36O2
Molecular weight	284.48 g/mol.
Description	Stearic acid is a hard white or faintly yellow – colored, somewhat glossy, crystalline solid or a white or yellowish white powder. It has a slight odour and taste suggesting tallow.
Functional categories	Emulsifying agent, solubilizing agent, tablet and capsule lubricant
Solubility	Freely soluble in benzene, carbon tetrachloride, chloroform and ether. Soluble in ethanol (95%), hexane and propylene glycol. Practically insoluble in water
Melting point	69.6°C
Stability and storage conditions	Stearic acid is a stable material. An antioxidant may also be added to it. The bulk material should be stored in a well – closed container in a cool, dry place.
Incompatibilities	Stearic acid is incompatible with most metal hydroxides and may be incompatible with oxidizing agents.
Applications	It aids dispersion of pigments and fillers.

	It acts as a stock lubricant

PRE GELATINIZED STARCH[38]

Table No: 8 Pre Gelatinized Starch excipients Profile

Non-proprietary Names	Amylum, polysaccharide
Synonyms	Starch 1500, starch LM
Empirical formula	$(C_6H_{10}O_5)_n$
Molecular weight	Depends on extent of gelatinization
Description	White color, odourless, tasteless
Functional Categories	Thickening agent, stiffening or gluing agent
Solubility	Insoluble in cold water or alcohol, Becomes soluble in water on heating
Stability and storage conditions	Starch is stable and should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Incompatible with strong acids, alkali. Avoid mixing with strong oxidizing materials.
Applications	Binder, Disintegrant, flow aid, lubricant.

SODIUM LAURYL SULPHATE[38]

Table No: 9 Sodium Lauryl Sulphate excipients Profile

Non-proprietary Names	Sodium dodecyl sulfate (SDS or NaDS), sodium laurilsulfate
Synonyms	Sodium monododecyl sulfate; Sodium lauryl sulfate; Sodium monolauryl sulfate; Sodium dodecanesulfate; dodecyl alcohol, hydrogen sulfate, sodium salt; n-dodecyl sulfate sodium; Sulfuric acid monododecyl ester sodium salt
Empirical formula	$NaC_{12}H_{25}SO_4$
Molecular weight	288.38 g mol^{-1}
Description	It is an anionic surfactant used in many cleaning and hygiene products. The salt is of an organosulfate consisting of a 12-carbon tail attached to a sulfate group, giving the material the amphiphilic properties required of a detergent.
Functional categories	Surfactant to remove oil stains, aid in lysing cells during DNA extraction
Solubility	Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.
Melting point	206°C

Stability and storage conditions	The bulk material should be stored in a well-closed container in a cool, dry place
Incompatibilities	Sodium lauryl sulphate is incompatible with strong oxidizing agents
Applications	found in toothpastes, shampoos, shaving foams, and bubble bath formulations in part for its thickening effect and its ability to create a lather

SODIUM STARCH GLYCOLATE[37]

Table No: 10 Sodium Starch Glycolate excipients Profile

Non-proprietary Names	Explotab, vivastar
Synonyms	Sodium salt of carboxymethyl ether of starch
Empirical formula	C_2H_5ONa
Molecular weight	500000 – 11000000
Description	White to off-white, tasteless, odorless, relatively free flowing powder.

Functional categories	Disintegrant, Dissolution aid, Suspending agent
Solubility	Practically insoluble in organic solvents. Absorbs water rapidly.
Melting point	338^0C
Stability and storage conditions	Store in well closed container to protect from humidity
Incompatibilities	Mostly compatible with all other tableting ingredients
Applications	Suspending and gelling agent

COLLOIDAL SILICON DIOXIDE[38]

Table No: 11 Colloidal Silicon Dioxide excipients Profile

Non-proprietary Names	Aerosil, cab-o-sil
Synonyms	Silica gel, silica sols, precipitated silica
Empirical formula	Polymer with multiple units of $Si(OH)_4$

Molecular weight	Depends on length of polymer chain
Description	Mono disperse or poly disperse suspension with particle size ranging from 30 to 100 nm
Functional categories	Glidant, Binder, catalyst, moisture absorption
Solubility	Practically insoluble in water, dilute acids, and most organic solvents.
Melting point	1600 - 1725°C
Stability and storage conditions	Colloidal solution is stabilized by pH adjustment and concentrated by evaporation
Incompatibilities	Incompatible with strong oxidizing agents
Applications	Flow promoter, glidant, lubricant

6. METHODOLOGY

6.1 PRE-FORMULATION STUDIES

Pre-formulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

A) Physiochemical evaluation of drug molecule:

1) Description.

2) Solubility.

3) pH.

4) Melting point.

5) Chemical nature.

6) Hygroscopicity.

7) Loss on drying.

8) Particle size determination.

9) Flow properties.

B) Compatibility Studies of the Drug with Excipients:

The information obtained from Preformulation studies indicates many of the subsequent events and approaches to be taken into consideration during formulation development.

A) PHYSIOCHEMICAL PARAMETERS[35,37,42]:

1) Description

It is the initial evaluation during Preformulation studies which assess the color and odor of the substance. This was only a descriptive test.

2) Solubility

Acetaminophen is classified under class III according to BCS i.e; highly soluble but low permeable. Methocarbamol is class II drug with low solubility and good permeability Solubility studies were conducted at all pH ranges from 1 to 7.4. The solubility of API was determined by dissolving the highest unit dose of the drug in 250 mL of buffer adjusted between pH 1.0 and 7.4. For this purpose 0.1N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and Purified water were used. Highest dose of the drug i.e., 500mg was dissolved in 250 mL of medium and was kept untouched for 12 hrs. Later on the insoluble drug was filtered off and the solution was analysed by HPLC technique to find out the solubility.

3) pH:

The pH is the measure of negative logarithm of hydrogen ion concentration of an aqueous solution. It is one of the most important factors from which the stand point of solubility, stability and physiochemical suitability of a formulation. The pH value of a solution is determined potentiometrically by means of a glass electrode.

4) Melting point

The temperature at which the first particle of the substance completely melts is regarded as melting point of the substance. The temperature at which the first particle starts to melt and last particle completely melts is regarded as the melting range.

5) Chemical nature

Solubility, stability, bioavailability etc., of a substance is depends on its chemical nature and this information helps to design a suitable dosage form.

6) Hygroscopicity

It is defined as ability of a substance to absorb moisture from the environment it exposed.

Table No: 12 Moisture Absorption Analysis

S.No	NATURE OF SAMPLE	RESULT OF THE DETERMINATION.
1	Deliquescent	Sufficient water absorbed to form a liquid.
2	Very hygroscopic	Increases in mass equal to or more than 15%.
3	Hygroscopic	Increases in mass less than 15% and equal to or more than 2%.
4	Slightly hygroscopic	Increases in mass less than 2% and equal to or more than 0.2%.

7) Loss on drying

0.5g of sample of was accurately weighed and the powder was kept in a moisture balance apparatus for 5 min. at 106^0C and the moisture content was calculated.

8) Particle size determination

Grain Size Determination

Particle size distribution is an important factor which determines number of parameters like dissolution rate, bioavailability, content uniformity, flow properties, texture and stability of a formulation. The particle size can be analyzed by number of methods like sieving, microscopic, laser diffraction methods etc, the particle size of Atorvastatin calcium and nicotinic acid was done by sieving method.

Sieve analysis:

Table No: 13 Classification of Sample Based on The % of Sample Retained or Passed on Test Sieves.

S.No	NATURE OF SAMPLE	RESULT OF DETERMINATION
1	Coarse powder	NLT 95% of the sample mass pass through 14# and NMT 40% pass through 36#
2	Moderately coarse powder	NLT 95% of the sample mass pass through 25# and NMT 40% pass through 60#
3	Moderately fine powder	NLT 95% of the sample mass pass through 36# and NMT 40% pass through 100#
4	fine powder	NLT 95% of the sample mass pass through 100# and NMT 40% pass through 150#
5	Very fine powder	NLT 95% of the sample mass pass through 150# and NMT 40% pass through 200#
6	Super fine powder	NLT 90% by number of particle are less than 10μm

9) Flow Property Measurement:

It is a very important parameter to be measured, since it affects the mass of uniformity of the dose. It is usually predicted in terms of angle of repose, bulk density and tapped density.

Angle of Repose

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

$$= \text{Tan}^{-1} h / r$$

Where

θ = angle of repose,

h = height,

r = radius.

A funnel was fixed at a height approximately of 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of the powder formed. Determine the angle of repose by measuring the height of the cone of powder and radius of the heap of powder.

Table No: 14 Flow Properties and corresponding angle of repose

S.No	FLOW PROPERTY	ANGLE OF REPOSE (DEGREES)
1	Excellent	25-30
2	Good	31-35
3	Fair	36-40
4	Passable	41-45
5	Poor	46-55
6	Very Poor	56-65
7	Very Very Poor	> 66

Bulk Density (BD) and Tapped Density (TD)

Bulk density of a compound varies substantially with the method of crystallisation, milling or formulation. It is of great importance when one considers the size of a high – dose capsule product or the homogeneity of a low dose formulation in which there are large differences in drug and excipient densities. In addition to bulk density, it is frequently desirable to know the true density of a powder for computation of void volume or porosity of packed powder beds.

An accurately weighed quantity of the granules/ powder was carefully poured into the graduated cylinder and volume was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 500 taps and after that the volume was measured and continued operation till the two consecutive readings were equal. The bulk density and the tapped density were calculated using the following formulae.

Bulk density = weight of sample in gram /volume occupied by the sample

Tapped density = Wt. of sample in gm / Tapped volume

Compressibility Index (CI) and Hausner ratio (HR)

The compressibility index and Hausner ratio methods are used for predicting powder flow characteristics. Both the compressibility index and the Hausner ratio were determined by using bulk density and the tapped density of a powder.

C.I=tapped-untapped*100/tapped

H.R=tapped density/bulk density.

Table No: 15 Relation of flow property with Hausners ratio & Compressibility Index

Compressibility Index (%)	Flow Character	Hauser's Ratio
≤10	Excellent	1. 00–1. 11
11–15	Good	1. 12–1. 18
16–20	Fair	1. 19–1. 25
21–25	Passable	1. 26–1. 34
26–31	Poor	1. 35–1. 45
32–37	Very poor	1. 46–1. 59
>38	Very, very poor	>1. 60

6.2 MATERIALS AND EQUIPMENTS

Table No: 16 List of materials for preparation of Acetaminophen

S.No.	Name of Materials used	Specification	Use
1.	Acetaminophen	IP	Active Ingredient
2.	Microcrystalline Cellulose	IP	Diluent

3	Pre gelatinized Starch	IP	Dry Binder
4.	Povidone K30	USP/NF	Binder
5.	Stearic acid	IP	Lubricant
6.	Sodium starch glycolate	USP/NF	Super disintegrant
7.	Purified Water	IP	Solvent

Table No: 17 List of materials for preparation of Methocarbamol

S.No.	Name of Materials used	Specification	Use
1.	Methocarbamol	IP	Active Ingredient
2.	Microcrystalline Cellulose	IP	Diluent
3	Pre gelatinized starch	USP/NF	Dry binder
4.	Povidone k30	USP/NF	Binder
5.	Sodium lauryl sulphate	IP	Surfactant
5.	Colloidal Silicon dioxide	IP	Glidant
6.	Magnesium Stearate	IP	Lubricant
7.	Colour lake of sunset yellow	IH	Coloring agent
8.	F D & C Blue	IH	Coloring agent

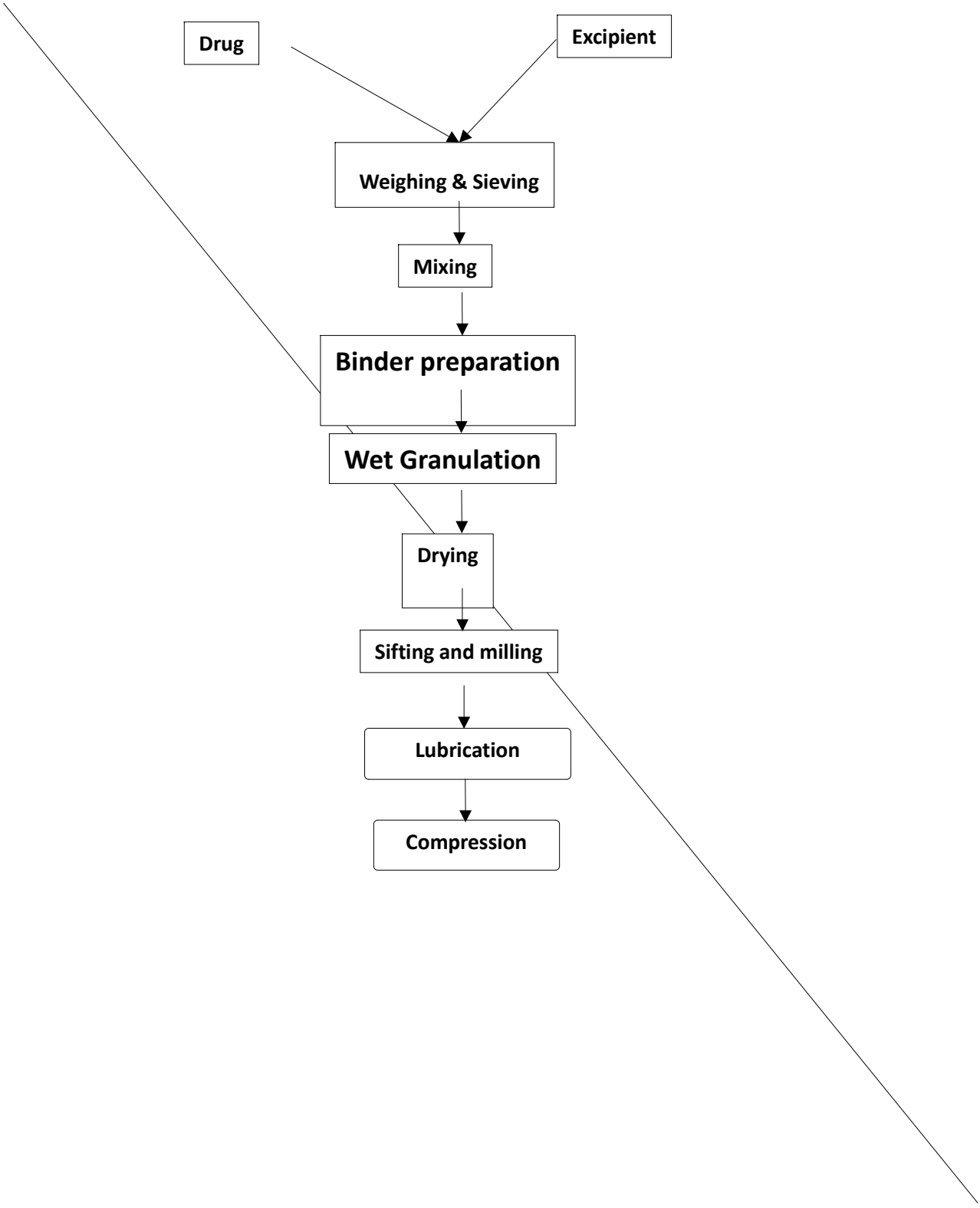
Table No: 18 List of Equipments used for formulation of tablets

S.No.	INSTRUMENTS USED	MANUFACTURER
1.	Electronic weighing balance, 210gm	Mettler, Bangalore
2.	Electronic weighing balance, 1 kg	Mettler, Bangalore
3	Sifter	Neomachine, Calcutta, India.

4.	Rapid mixture granulator	Tapasya, Mumbai, India
5.	Fluidized bed dryer	Tapasya, Mumbai, India
6.	Multi mill	Neomachine, Calcutta, India
7.	Blender	Vamp, India
8.	Tablet compression machine 16 station single rotary	Cadmach, Ahmedabad
9.	Automatic tablet dissolution apparatus USP II	vanket, USA
10	Electronic thickness measurement apparatus	Mituoyo, japan
11	Friability tester	Electrolab, Mumbai, India)
12	Tablet hardness tester	Schleuniger, USA
13	Electronic LOD measurement apparatus	Sartorius, Germany
14	Bulk density apparatus	Electrolab, Mumbai, India
15	HPLC	Shimadzu ,Mumbai, India
16	FT-IR spectrophotometer	Shimadzu, Mumbai, India

6.3 PROCESS INVOLVED IN BI-LAYER TABLET PRODUCTION

Figure No: 3 Flow Chart process involved in bi-layer tablet production


Drug
Excipient
Weighing & Sieving
Mixing
Binder preparation
Wet Granulation
Drying
Sifting and milling
Lubrication
Compression

Steps Involved in Formulation of Methocarbamol granules

Take 54kg of water (temp 65ºC) in 100L stainless steel vessel. Then dissolve 0.72kg of povidone k-30 by stirring with stainless steel paddle. Then add D & C yellow ≠ 10 of 0.019kg and F D & C blue # 1 of 0.0075kg. then disperse Sodium laurel sulfate 0.240 in 5kg of water separately in small vessel and add to above povidone solution slowly.

Dry mixing: - Check weight of methocarbamol and sift through 12# mesh and sift pre-gelatinized starch and methyl cellulose through 40# mesh load in to rapid mixer granulation. Dry mix for 10min at low speed.

Granulation:- Add binder solution to above powder which mixing for 5-10min at mill slow speed. Change mill speed to fast and mix for 5-15min till required end point achieved. If required add up to 4kg additional water through rapid mixer granulation man hole. Switch granulator at fast speed and mix for 1-2min. pass the wet mass through co-mill attached to rapid mixer granulation while mixer at deep speed and granulator at slow speed. And unload into Fluidized bed dryer bowl. Scrap material from rapid mixer granulation bowl and Fluidized bed dryer bowl at end of batch. Record additional water quantity and record ampelage achieved on.

Drying :- Dry the wet milled granules in Fluidized bed dryer for 10min.Rake and check for loss on drying carry on drying for 10min and rake again. Dry till loss on drying at 0.6 - 1.2% achieved. Check loss on drying at 90ºC in halogen moisture balance.

Sifting and Dry mixing: - Pass the dried granules into double vibratory sifter. Collect the good fraction of granules passing through # 14/150 mesh through metal detector loads the granules and fines into the octagonal blender. Mill the sieve tops retained over # 14 mesh through 2.0mm screen using comminuting mill, knives forward and medium speed. Pass the miller granule through # 14 on double deck sifter. Collect all the granules passing through #14 through metal detector and load the granules into the octagonal blender.

Blending: - Load the granules in octagonal blender and blend for 5min at 6rpm. Add sifter sodium starch glycolate, micro crystalline cellulose, colloidal silicon through #40 mesh to octagonal blender. Add sifted magnesium stearate through #40 mesh to octagonal blender and blend for 5min at 6rpm.

6.4 Formulation Development Comparative data of various formulations of Methocarbamol

Trial-1

Table No: 19 Formula of Methocarbamol Trial-1

S. No	Ingredients	Quantity
1	Methocarbamol	332mg

2	Pregelatinised starch	16.1mg
3	Microcrystalline cellulose	20mg
4	PVP K 30	1.6mg
5	D&C yellow#10	0.02mg
6	FD&C Blue#2	0.3mg
7	Ferric oxide red	0.4mg
8	Micro crystalline cellulose	14.7mg
9	Sodium starch glycolate	12mg
10	Colloidal silicon di oxide	0.48mg
11	Magnesium stearate	2.4mg
	Total % composition	400mg

Trial-2

Table No: 20 Formula of Methocarbamol Trial-2

S. No	**Ingredients**	**Quantity**
1	Methocarbamol	332mg
2	Pregelatinised starch	15.7mg

3	Microcrystalline cellulose	20mg
4	PVP K 30	2mg
5	D&C yellow#10	0.02mg
6	FD&C Blue#2	0.3mg
7	Ferric oxide red	0.4mg
8	Micro crystalline cellulose	14.7mg
9	Sodium starch glycolate	12mg
10	Colloidal silicon di oxide	0.48mg
11	Magnesium stearate	2.4mg
	Total % composition	400mg

Trial-3

Table No: 21 Formula of Methocarbamol Trial-3

S. No	**Ingredients**	**Quantity**
1	Methocarbamol	332mg

2	Pregelatinised starch	14.6mg
3	Microcrystalline cellulose	20mg
4	PVP K 30	1.6mg
5	D&C yellow#10	0.02mg
6	FD&C Blue#2	0.8mg
7	Ferric oxide red	1.4mg
8	Micro crystalline cellulose	14.7mg
9	Sodium starch glycolate	12mg
10	Colloidal silicon di oxide	0.48mg
11	Magnesium stearate	2.4mg
	Total % composition	400mg

Trial-4

Table No: 22 Formula of Methocarbamol Trial-4

S. No	**Ingredients**	**Quantity**

1	Methocarbamol	332mg
2	Pregelatinised starch	14mg
3	Microcrystalline cellulose	20mg
4	PVP K 30	1.6mg
5	D&C yellow#10	0.02mg
6	FD&C Blue#2	1mg
7	Ferric oxide red	1.8mg
8	Micro crystalline cellulose	14.7mg
9	Sodium starch glycolate	12mg
10	Colloidal silicon di oxide	0.48mg
11	Magnesium stearate	2.4mg
	Total % composition	400mg

Trial-5

Table No: 23 Formula of Methocarbamol Trial-5

S. No	**Ingredients**	**Quantity**

1	Methocarbamol	332mg
2	Pregelatinised starch	14.6mg
3	Microcrystalline cellulose	20mg
4	PVP K 30	1.6mg
5	D&C yellow#10	0.02mg
6	FD&C Blue#2	1mg
7	Ferric oxide red	1.2mg
8	Micro crystalline cellulose	14.7mg
9	Sodium starch glycolate	12mg
10	Colloidal silicon di oxide	0.48mg
11	Magnesium stearate	2.4mg
	Total % composition	400mg

Trial-6

Table No: 24 Formula of Methocarbamol Trial-6

S. No	**Ingredients**	**Quantity**

1	Methocarbamol	332mg
2	Pregelatinised starch	14.4mg
3	Microcrystalline cellulose	20mg
4	PVP K 30	1.6mg
5	D&C yellow#10	0.02mg
6	FD&C Blue#2	1mg
7	Ferric oxide red	1.2mg
8	Sodium lauryl sulphate	0.2mg
9	Micro crystalline cellulose	14.7mg
10	Sodium starch glycolate	12mg
11	Colloidal silicon di oxide	0.48mg
12	Magnesium stearate	2.4mg
	Total % composition	400mg

Trial-7

Table No: 25 Formula of Methocarbamol Trial-7

S. No	Ingredients	Quantity
1	Methocarbamol	332mg
2	Pregelatinised starch	14.2mg
3	Microcrystalline cellulose	20mg
4	PVP K 30	1.6mg
5	D&C yellow#10	0.02
6	FD&C Blue#2	1mg
7	Ferric oxide red	1.2mg
8	Sodium lauryl sulphate	0.4mg
9	Micro crystalline cellulose	14.7mg
10	Sodium starch glycolate	12mg
11	Colloidal silicon di oxide	0.48mg
12	Magnesium stearate	2.4mg
	Total % composition	400mg

Trial-8

Table No: 26 Formula of Methocarbamol Trial-8

S. No	Ingredients	Quantity
1	Methocarbamol	332mg
2	Pregelatinised starch	13.8mg
3	Microcrystalline cellulose	20mg
4	PVP K 30	1.6mg
5	D&C yellow#10	0.02mg
6	FD&C Blue#2	1mg
7	Ferric oxide red	1.2mg
8	Sodium lauryl sulphate	0.8mg
9	Micro crystalline cellulose	14.7mg
10	Sodium starch glycolate	12mg
11	Colloidal silicon di oxide	0.48mg
12	Magnesium stearate	2.4mg
	Total % composition	400mg

Trial-9

Table No: 27 Formula of Methocarbamol Trial-9

S. No	Ingredients	Quantity
1	Methocarbamol	332mg
2	Pregelatinised starch	13.8mg
3	Microcrystalline cellulose	20mg
4	PVP K 30	1.6mg
5	D&C yellow#10	0.02mg
6	FD&C Blue#2	1mg
7	Ferric oxide red	1.2mg
8	Sodium lauryl sulphate	0.8mg
9	Micro crystalline cellulose	14.7mg
10	Sodium starch glycolate	12mg
11	Colloidal silicon di oxide	0.48mg
12	Magnesium stearate	2.4mg
	Total % composition	400mg

Steps Involved in Formulation of Acetaminophen granules

Take 54kg of water (temp 65ºC) in 100L stainless steel vessel. Then dissolve 0.72kg of povidone k-30 by stirring with stainless steel paddle. then disperse sodium starch glycolate 0.240 in 5kg of water separately in small vessel and add to above povidone solution slowly.

Dry mixing: - check weight of acetaminophen and sift through 12# mesh and sift pre-gelatinized starch and methyl cellulose through 40# mesh load in to rapid mixer granulation. Dry mix for 10min at low speed.

Granulation:- Add binder solution to above powder which mixing for 5-10min at mill slow speed. Change mill speed to fast and mix for 5-15min till required end point achieved. If required add up to 4kg additional water through rapid mixer granulation man hole. Switch granulator at fast speed and mix for 1-2min. pass the wet mass through co-mill attached to rapid mixer granulation while mixer at deep speed and granulator at slow speed. And unload into Fluidized bed dryer bowl. Scrap material from rapid mixer granulation bowl and Fluidized bed dryer bowl at end of batch. Record additional water quantity and record ampelage achieved on.

Drying:- Dry the wet milled granules in Fluidized bed dryer for 10min.Rake and check for loss on drying carry on drying for 10min and rake again. Dry till loss on drying at 0.6 - 1.2% achieved. Check loss on drying at 90ºC in halogen moisture balance.

Sifting and Dry mixing: - Pass the dried granules into double vibratory sifter. Collect the good fraction of granules passing through # 14/150 mesh through metal detector loads the granules and fines into the octagonal blender. Mill the sieve tops retained over # 14 mesh through 2.0mm screen using comminuting mill, knives forward and medium speed.

Pass the miller granule through # 14 on double deck sifter. Collect all the granules passing through #14 through metal detector and load the granules into the octagonal blender.

Blending: - Load the granules in octagonal blender and blend for 5min at 6rpm. Add sifter sodium starch glycolate, micro crystalline cellulose, colloidal silicon through #40 mesh to octagonal blender. Add sifted stearic acid through #40 mesh to octagonal blender and blend for 5min at 6rpm.

6.5 Comparative data of various formulations of Acetaminophen

Trial-1

Table No: 28 Formula of Acetaminophen Trial-1

S. No	Ingredients	Quantity
1	Acetaminophen	450mg
2	Microcrystalline cellulose	32.5mg
3	PVP K 30	5mg
4	Stearic acid	5mg
5	Total	500mg

Trial-2

Table No: 29 Formula of Acetaminophen Trial-2

S. No	Ingredients	Quantity
1	Acetaminophen	450mg
2	Microcrystalline cellulose	40mg
3	PVP K 30	5mg
4	Sodium starch glycolate	7.5mg
5	Stearic acid	5mg
6	Total	500mg

Trial-3

Table No: 30 Formula of Acetaminophen Trial-3

S. No	Ingredients	Quantity
1	Acetaminophen	450mg
2	Microcrystalline cellulose	30mg
3	PVP K 30	5mg
4	Sodium starch glycolate	10mg
5	Stearic acid	5mg
6	Total	500mg

Trial-4

Table No: 31 Formula of Acetaminophen Trial-4

S. No	Ingredients	Quantity
1	Acetaminophen	450mg
2	Microcrystalline cellulose	30mg
3	PVP K 30	5mg
4	Sodium starch glycolate	10mg
5	Stearic acid	5mg
6	Total	500mg

Trial-5

Table No: 32 Formula of Acetaminophen Trial-5

S. No	Ingredients	Quantity
1	Acetaminophen	450mg
2	Pregelatinised starch	2.5mg
3	Microcrystalline cellulose	30mg
4	PVP K 30	2.5mg
5	Sodium starch glycolate	10mg
6	Stearic acid	5mg
7	Total	500mg

Trial-6

Table No: 33 Formula of Acetaminophen Trial-6

S. No	Ingredients	Quantity
1	Acetaminophen	450mg
2	Pregelatinised starch	10mg
3	Microcrystalline cellulose	22.5mg
4	PVP K 30	2.5mg
5	Sodium starch glycolate	10mg
6	Stearic acid	5mg
7	Total	500mg

Trial-7

Table No: 34 Formula of Acetaminophen Trial-7

S. No	Ingredients	Quantity
1	Acetaminophen	450mg
2	Pregelatinised starch	20mg
3	Microcrystalline cellulose	12.5mg
4	PVP K 30	2.5mg
5	Sodium starch glycolate	10mg
6	Stearic acid	5mg
7	Total	500mg

Trial-8

Table No: 35 Formula of Acetaminophen Trial-8

S. No	Ingredients	Quantity
1	Acetaminophen	450mg
2	Pregelatinised starch	29.5mg
3	PVP K 30	2.5mg
4	Sodium starch glycolate	10mg
5	Stearic acid	8mg
6	Total	500mg

Trial-9

Table No: 36 Formula of Acetaminophen Trial-9

S. No	Ingredients	Quantity
1	Acetaminophen	450mg
2	Pregelatinised starch	29.5mg
3	PVP K 30	3mg
4	Sodium starch glycolate	7.5mg
5	Stearic acid	10mg
6	Total	500mg

Moisture content: - [by karl fisher method]

Transfer 35-40ml of methanol to the titration vessel and titrate with the reagent to the electrometric or visual end point to consume any moisture that may be present. Grind 10tabs to a fine powder in dry mortar. Weigh accurately between 0.2-0.5gm of powdered sample, and quickly add to the titration vessel and perform the test potentiometrically.

6.6 COMPRESSION OF BI LAYER TABLETS:

6.6.1 Compression Parameters:-

Compression is done by using SEJONG 49 station compression machine specially designed for the compression of bi layer tablets having two different hoppers for the flow of granules of two drugs.Two punches are set in the compression machine for the compression of two layers. First acetaminophen layer undergoes slight initial compression under low hardness and then the methocarbamol granules are filled in the die cavity and the final compression takes place with desired weight and hardness being set.

Weight and the content uniformity of the two layers in the tablet are tested

6.6.2 Punch specifications:-

Upper punch – upper punches 19.1 X 8.9mm caplet shape, concave punches-embossing with 'E/S'.

Lower punch- lower punches 19.1 X 8.9mm caplet shape, concave punches-embossing with '255'.

Dies - 19.1 X 8.9mm bore size. 'B' tooling

Temperature and relative humidity record

Temperature- 24-25ºC

RH- 50-51%

6.6.3 Compression Parameters:-

Description of tablet - white and green coloured, caplet shape bilayer tablets with 255 engraving on white side and ES engraving on green side with score line between ES.

Weight of white layer [acetaminophen] - 555.0mg±5% [527.3mg-582.8mg]

Weight of green layer [methocarbamol] - 482.0mg±5% [457.9mg-506.1mg]

Weight of 20 tablets – 20.74gm±2% [20.33gm-21.15gm]

Hardness – NLT 10kp

Thickness – 6.9mm±0.3mm

Friability – NMT 0.8% w/w

Disintegration time – NMT 15min

Individual tablet weight variation – 1037mg±5% [985.0mg – 1089.0mg]

6.7 COATING PROCEDURE OF THE TABLETS:

Coating is done in the GLATT tablet hi coater with the optimized parameters for uniform coating of the tablets without any rough service on the tablet and uniformity in the coating is achieved by stirring the coating solution continuously during coating and the percentage of coating is properly checked by taking the average initial weight of 50 tablets before coating and after coating

6.7.1 Coating parameters:-

Inlet temperature – 70-80ºC

Exhaust temperature – 40-50ºC

Atomisation pressure – 3.0-4.0kg/cm^2

Pan-rpm – 2.4rpm

Gun-bed distance – 20-30cm

Spray rate – 180-250ml/min/4guns

Peristal pump rpm – 15-16rpm

Preparation of coating solution:-

Take purified water having ambient temperature[15-35ºC] into a stainless steel vessel.

Check weight of advantia prime 199900BA01[18.85±0.1kg].

Stir purified water with stirrer to form vortex add advantia prime into vortex slowly.

Reduce the stirrer speed, so that no vortex should form and continue for 30-45min

6.8 POST COMPRESSION PARAMETERS:

The quantitative evaluation and assessment of a tablet's chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. These properties are important since chemical breakdown or interactions between tablet components may alter the physical tablet properties, and greatly affect the bioavailability of the tablet system. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters. The diameters and shape depends on the die and punches selected for the compression of tablets. The remaining specifications assure that tablets do not vary from one production lot to another. The following standards or quality control tests should be carried out on compressed tablets.

1. General appearance

The general appearance of tablets, its visual identity and overall 'elegance' is essential for consumer acceptance, control of lot-to-lot uniformity and general tablet-to-tablet uniformity and for monitoring the production process. The control of general appearance involves measurement of attributes such as a tablet's size, shape, color, presence or absence of odor, taste, surface textures, physical flaws and consistency.

2. Size and shape

The type of tooling determines the shape and dimensions of compressed tablets during the compression process. At a constant compressive load, tablets thickness varies with changes in die fill, particle size distribution and packing of the powder mix being compressed and with tablet weight, while with a constant die fill, thickness varies with variation in compressive load. Tablet thickness is consistent from batch to batch or within a batch only if the tablet granulation or powder blend is adequately consistent in particle size and particle size distribution, if the punch tooling is of consistent length, and if the tablet press is clean and in good working condition.

3. Thickness

The thickness of individual tablets may be measured with a micrometer, which permits accurate measurements and provides information of the variation between tablets. Tablet thickness should be controlled within a ± 5% variation of a standard value. Any variation in thickness within a particular lot of tablets or between manufacturer's lots should not be apparent to the unaided eye for consumer acceptance of the product. In addition, thickness must be controlled to facilitate packaging.

The physical dimensions of the tablet along with the density of the material in the tablet formulation and their proportions, determine the weight of the tablet. The size and shape of the tablet can also influence the choice of tablet machine to use, the best particle size for granulation, production lot size that can be made, the best type of tableting processing that can be used, packaging operations, and the cost of production.

4. Weight variation

This test is also known as uniformity of weight. This does not apply to layer or enteric coated tablets. Weights of individual 20 tablets was noted and their mean weight was calculated, and the percentage deviation was calculated by using the formula

$$\text{Percentage deviation} = \frac{X - X^1}{X} \times 100$$

Where,

X = actual weight of the tablet

X^1 = average weight of the tablet

5. Content uniformity

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets and all capsules intended for oral administration where the ranges of size of the dosage form available include 50mg or smaller sizes. Tablet monographs with a content uniformity requirement do not have weight variation requirements4. For content uniformity test, representative samples of 30tablets are selected and 10 are assayed individually. At least 9 must assay within ±15% of the declared potency and none may exceed ± 25%.

6. Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. Normally, when capping occurs, friability values are not calculated. A thick tablet may have fewer tendencies to cap whereas thin tablets of large diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress.

$$\text{Friability index} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}}$$

7. Hardness

The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. It is now designated as either the Monsanto or Stokes hardness tester. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrally to the tablet.

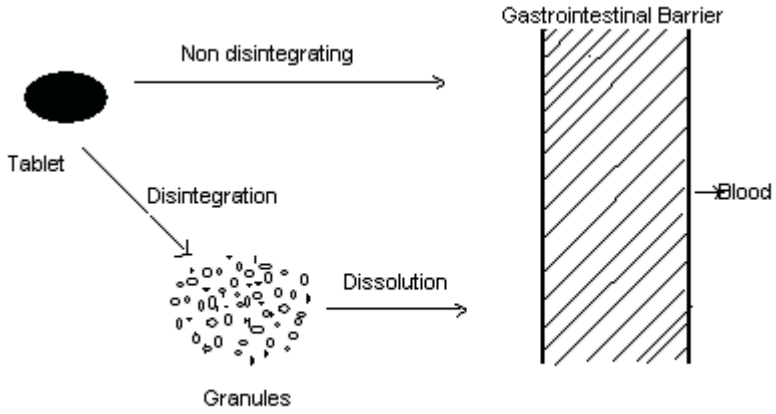
Hardness, which is now more appropriately called crushing strength determinations are made during tablet production and are used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets2. Oral tablets normally have a hardness of 4 to 10kg; however, hypodermic and chewable tablets are usually much softer (3 kg) and some sustained release tablets are much harder (10-20 kg). Tablet hardness has been associated with other tablet properties such as density and porosity. Hardness generally increases with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression.

8. Dissolution

Dissolution is the process by which a solid solute enters a solution. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition.

Dissolution behavior of drugs has a significant effect on their pharmacological activity. In fact, a direct relationship between in vitro dissolution rate of many drugs and their Solid dosage forms may or may not disintegrate when they interact with gastrointestinal fluid following oral administration depending on their design.

Figure No: 4 Schematic diagram of the dissolution process



Dissolution kinetics is important in determining the bioavailability of a drug. Levy and some other workers reported that the dissolution rate controls the rate of build up of certain drugs in the blood stream. It was thus recognized that in-vitro dissolution kinetics provides useful information on the availability of drugs and their subsequent therapeutic effects in-vivo. The various pharmacopoeias contain specifications on the dissolution requirements of various drugs. A variety of designs of apparatus for dissolution testing have been proposed and tested, varying from simple beaker with stirrer to complex systems with lipid phases and lipid barrier where an attempt is made to mimic the biological milieu. The choice of the apparatus to be used depends largely on the physicochemical properties of the dosage form.

Two types of methods are employed for performing the in vitro dissolution studies

1. Basket type
2. Paddle type

1. Basket type

Basket method is used for evaluating the formulations that tend to float while carrying out the dissolution study. Floating can be due to swelling of the formulation by taking some amount of dissolution media which makes the formulation lighter than the dissolution medium. So, in this method the formulation is entrapped inside the basket that will not allow the formulation to float even if it swells and becomes lighter than the dissolution medium.

2. Paddle type

Paddle method can be used for floating formulations and those formulations that don't float even after swelling. The dissolution apparatus consists of a cylindrical vessel made of glass or inert transparent material. The volume of the vessel generally used was 900 ml. In the vessel dissolution media was taken and the formulation to be evaluated had to be placed in it. A shaft is present which is connected at one end to a motor and the other end to a basket or paddle according to the method employed.

For basket method unless otherwise specified 40-mesh size for the basket was used. The rpm of the shaft was 100 rpm for basket method and 50 rpm for paddle method. In regular intervals of time samples were withdrawn from the vessel and analyzed for the drug release up to each interval by UV Visible spectrophotometer. After withdrawing the sample it was replaced with same amount of dissolution medium to maintain sink conditions.

8.1 Dissolution for Acetaminophen

Medium : 900 ml of phosphate buffer pH 5.8

RPM : 50

Time : 5, 10, 15, 30, 45, 60.

Apparatus : Paddle.

Temperature : 37^0 C ± 0.5^0 C

Preparation of buffer pH 5.8

Solution A: 0.2M Monobasic potassium phosphate(KH2PO4):

Weigh about 27.22gm of potassium di hydrogen phosphate in 1000 ml volumetric flask and dissolve in 300ml of purified water and make up to volume with purified water.

Solution B: 0.2M Sodium hydroxide solution:

Weigh about 0.8gm of sodium hydroxide pellets in 100ml volumetric flask add 60ml of purified water and dissolve. Make up to volume with purified water.

Dissolution Medium preparation (USP Phosphate buffer pH 5.8):

Take 250ml of solution A and add 18ml solution B , make up to the volume of 1000ml with purified water. Adjust the pH 5.8+/- 0.05 with 0.2M sodium hydroxide solution if necessary.

Sample Preparation

Place one tablet in each of the 6 bowls containing 900ml of media that has been equilibrated to 37°c+/-0.5 Take care to exclude air bubbles from surface of tablet. Withdraw 10ml of sample after completion of 5min from each dissolution bowl. After withdrawal of sample replace 10ml of Buffer pH 5.8 maintained at $37^0 \pm 0.5^0$ C. Follow the same procedure after completion of 10, 15, 30, 45min. Samples are withdrawn from a zone midway between surface of dissolution medium and top of rotating paddle, not less than 1cm from the vessel wall and filter through Millex – HV 0.45micron PVDF filter, and inject solution directly in to HPLC.

Standard Preparation

Weigh accurately about 55.0 mg of Acetaminophen working Standard and transfer to a 100 ml volumetric flask shake with sufficient dissolution medium, sonicate to dissolve and make up the volume with dissolution media. Filter through 0.45 micron HDPE filter.

Procedure:

Separately inject equal volumes of Mobile phase, Blank (Dissolution media), standard (Five replicate injections) and sample preparation, record the chromatograms, and measure the areas for the Acetaminophen. Calculate the quantity of acetaminophen.

System suitability:

Chromatograph the standard preparation, and record the peak responses as directed

1) The relative standard deviation for five replicate injections of standard of Acetaminophen is not more than 2%
2) Tailing factors for Acetaminophen peak are not more than 2

Calculation:

$$\frac{TA}{SA} \times \frac{SW}{100} \times \frac{900}{L.A} \times \frac{P}{100} \times 100$$

Where,

SA = Peak area due to Acetaminophen in standard preparation

TA = Peak area due to Acetaminophen in sample preparation

SW = Weight of Acetaminophen working standard in mg

P = Purity of Acetaminophen working standard

L.A = Labeled amount of acetaminophen in mg

8.2 Dissolution for Methocarbamol:

Standard Preparation

Weigh accurately about 44.0 mg of Methocarbamol working Standard and transfer to a 100 ml volumetric flask shake with sufficient dissolution medium, sonicate to dissolve and make up the volume with dissolution media. Filter through 0.45 micron HDPE filter.

Procedure:

Separately inject equal volumes of Mobile phase, Blank (Dissolution media), standard (Five replicate injections) and sample preparation, record the chromatograms, and measure the areas for the Methocarbamol.

System suitability:

Chromatograph the standard preparation, and record the peak responses as directed

The relative standard deviation for five replicate injections of standard of Methocarbamol is not more than 2%

1) Tailing factors for Methocarbamol peak are not more than 2

Calculation:

$$\frac{TA}{SA} \times \frac{SW}{100} \times \frac{900}{L.A} \times \frac{P}{100} \times 100$$

Where,

SA = Peak area due to Methocarbamol in standard preparation

TA = Peak area due to Methocarbamol in sample preparation

SW = Weight of Methocarbamol working standard in mg

P = Purity of Methocarbamol working standard

L.A = Labeled amount of Methocarbamol in mg

9. DRUG CONTENT

Chromatographic conditions:

Column – L_1, 100*4.6mm,5µ

[Develosil ODS-MG-5,100*4.6,5µ is suitable]

Flow rate – 1.0mL/min

Wave length – 273nm

Injection volume - 140µL

Column oven temp - 25°C ± 2°C

Run time – 7min

Mobile phase:-

Prepare a mixture of milli Q water, methanol, glacial acetic acid in the ratio of 600:400:15. Filter through 0.45µ PVDF filter and degas.

Diluent preparation:-

Prepare a mixture of milli Q water and methanol in the ratio of 600:400. Filter through 0.45µ PVDF filter and degas.

Standard preparation:-

Accurate weigh and transfer of 50mg of acetaminophen and 40mg of Methocarbamol working standard in to a 200ml of volumetric flask, add sufficient amount of diluent, sonicate to dissolve and make up volume with diluent. Prepare the standard in duplicate [i.e standard 'A' and standard 'B'] and calculate the recovery of the standard B using the formula.

$$\frac{\text{Area of standard A}}{\text{Area of standard B}} * \frac{\text{Weight of standard B}}{\text{Weight of standard A}} * \text{purity of standard.}$$

Sample preparation:-

Weigh and finely powder not fewer than 20tabs. Transfer about 1047 mg of the powder equivalent to about 500mg of acetaminophen and 400mg of Methocarbamol into a 200ml volumetric flask. To it add 100ml of diluent. Sonicate for 30min and make up to volume with diluent. Filter the solution through 0.45µ miller HV PVDF. Further dilute 5ml to 50ml with diluent.

Procedure:-

Separately inject 10µL mobile phase. The blank [diluent] standard 'A' preparation [five replicate injections]. Standard 'B' preparation [duplicate injection] into the chromatograph. Record the chromatograms, and measure responses for the major peaks.

Calculate % release of acetaminophen and Methocarbamol comparing with standard A.

System suitable:-

Chromatograph the standard preparation and record the peak responses as directed.

1] The related standard deviation for five replicate injections of standard for both acetaminophen and Methocarbamol is not more than 2.0%.

2] The tailing factor for the acetaminophen and Methocarbamol peak are not more than 2.0.

Calculation:-

% of Acetaminophen =

$$\frac{TA}{SA} \times \frac{SW}{200} \times \frac{200}{TW} \times \frac{50}{5} \times \text{Avg.wt} \times \frac{P}{100} \times \frac{100}{LA}$$

Where,

TA = Peak area due to acetaminophen in sample preparation

SA = Peak area due to acetaminophen in standard preparation

SW = Weight of acetaminophen working standard in mg

P = Purity of acetaminophen working standard

LA = Labelled amount of acetaminophen in mg

TW = weight of sample taken in mg

% of Methocarbamol =

$$\frac{TA}{SA} \times \frac{SW}{200} \times \frac{200}{TW} \times \frac{50}{5} \times \text{Avg wt.} \times \frac{P}{100} \times \frac{100}{LA}$$

Where,

TA = Peak area due to methocarbamol in sample preparation

SA = Peak area due to methocarbamol in standard preparation

SW = Weight of methocarbamol working standard in mg

P = Purity of methocarbamol working standard

LA = Labelled amount of methocarbamol in mg

TW = weight of sample taken in mg

B) Drug Excipient Compatibility Study

The compatibility of drug and formulation components was important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

Procedure:

Drug was mixed with excipients in different ratio. These mixtures were kept in a 5ml glass white colored vials and packed properly. These vials are exposed to room temperature and 40˚c/75%RH. 2-3gm of blend was prepared which was filled in 3 vials. Observations for physical appearance were made at zero weeks, 1 month, the samples were withdrawn for analysis of appearance, moisture content, assay & related substance.

7. RESULTS AND DISCUSSION

7.1 PHYSIOCHEMICAL PARAMETERS:

1. DESCRIPTION:

Table No: 37 Description

S.No	RAW MATERIAL (API)	COLOUR	ODOUR	NATURE
1	**Acetaminophen**	White	Odour less	Crystalline powder
2	**Methocarbamol**	White	Odour less	Crystalline powder

2. SOLUBILITY:

Table No: 38 Solubility

S. No	RAW MATERIAL (API)	SOLUBILITY
1	**Acetaminophen**	Water - Slightly soluble Organic solvents - Soluble
2	**Methocarbamol**	Water - Sparingly soluble Chloroform - Sparingly soluble Propylene glycol - Soluble Benzene - Insoluble n-hexane - Insoluble

3. pH:

Table No: 39 pH

S.No	RAW MATERIAL (API)	SOLUTION CONCENTRATION	pH
1	**Acetaminophen**	1mg/ml	5.9
2	**Methocarbamol**	1mg/ml	5.4

4. MELTING POINT:

Table No: 40 Melting point

S. No	RAW MATERIAL (API)	OBSERVED VALUE
1	**Acetaminophen**	170.8°C
2	**Methocarbamol**	95.2°C

5. CHEMICAL NATURE:

Table No: 41 Acetaminophen & Methocarbamol specifications.

S.NO	PARAMETERS	ACETAMINOPHEN	METHOCARBAMOL
1	**Molecular formula**	$C_8H_9NO_2$	$C_{11}H_{15}NO_5$
2	**Molecular weight**	151.16	241.24
3	**IUPAC name**	N-(4 hydroxyphenyl)acetamide	3-(2-methoxyphenoxy)-1,2-propanediol 1-carbamate
4	**Chemical nature**	Synthetic, non opiate, centrally acting analgesic	Centrally acting anti inflamatory

6. HYGROSCOPICITY:

Table No: 42 Interpretation of results based on percent increase in mass.

S. No	RAW MATERIAL (API)	RESULT
1	**Acetaminophen**	Not hygroscopic
2	**Methocarbamol**	Not hygroscopic

7. LOSS ON DRYING:

Table No: 43 Loss on drying.

S. No	RAW MATERIAL (API)	OBSERVED LOD
1	**Acetaminophen**	0.22%
2	**Methocarbamol**	0.28%

8. SIEVE ANALYSIS:

Table No: 44 Sieve analysis.

S. No	RAW MATERIAL (API)	NATURE OF SAMPLE
1	**Acetaminophen**	Fine powder
2	**Methocarbamol**	Fine powder

9. FLOW PROPERTY MEASUREMENT:

- **ANGLE OF REPOSE:**

Table No: 45 Flow property and corresponding angle of repose.

S. No	RAW MATERIAL (API)	ANGLE OF REPOSE (DEGREES)	FLOW PROPERTY
1	**Acetaminophen**	41.2°	Very poor
2	**Methocarbamol**	40.81°	Very poor

- **DENSITY:**

  - **BULK DENSITY:**

Table No: 46 Bulk Density.

S. No	RAW MATERIAL (API)	BULK DENSITY (PI) (g/ml)
1	**Acetaminophen**	0.6
2	**Methocarbamol**	0.4

  - **TAPPED DENSITY:**

Table No: 47 Tapped Density.

S. No	RAW MATERIAL (API)	TAPPED DENSITY (Pt) (g/ml)
1	**Acetaminophen**	0.573
2	**Methocarbamol**	0.39

- **COMPRESSIBILTY INDEX:**

Table No: 48 Compressibilty Index.

S. No	RAW MATERIAL (API)	COMPRESSIBILTY INDEX (%)	FLOW PROPERTY
1	**Acetaminophen**	27.32	Poor
2	**Methocarbamol**	28.61	Poor

- **HAUSNER RATIO:**

Table No:49 Hausner's ratio.

S. No	RAW MATERIAL (API)	HAUSNER RATIO	FLOW PROPERTY
1	**Acetaminophen**	1.37	Poor
2	**Methocarbamol**	1.41	Poor

10. DRUG CONTENT:

Table No: 50 Drug Content

S. No	RAW MATERIAL (API)	ASSAY (%)
1	**Acetaminophen**	99.78
2	**Methocarbamol**	99.62

7.2 COMPATIBILITY STUDIES:

Table No: 51 Compatibility Studies of Acetaminophen With Excipients.

Drug	Excipients (Ratio= 1:1)	1st day 40^{0}C & 75% RH	1st week 40^{0}C & 75% RH	2nd week 40^{0}C & 75% RH	3rd week 40^{0}C & 75% RH
A	Methocarbamol	Nd	Nd	Nd	Nd
A	Pregelatinized starch	Nd	Nd	Nd	Nd
A	PVP K-30	Nd	Nd	Nd	Nd
A	Sodium Starch Glycolate	Nd	Nd	Nd	Nd
A	Stearic Acid	Nd	Nd	Nd	Nd

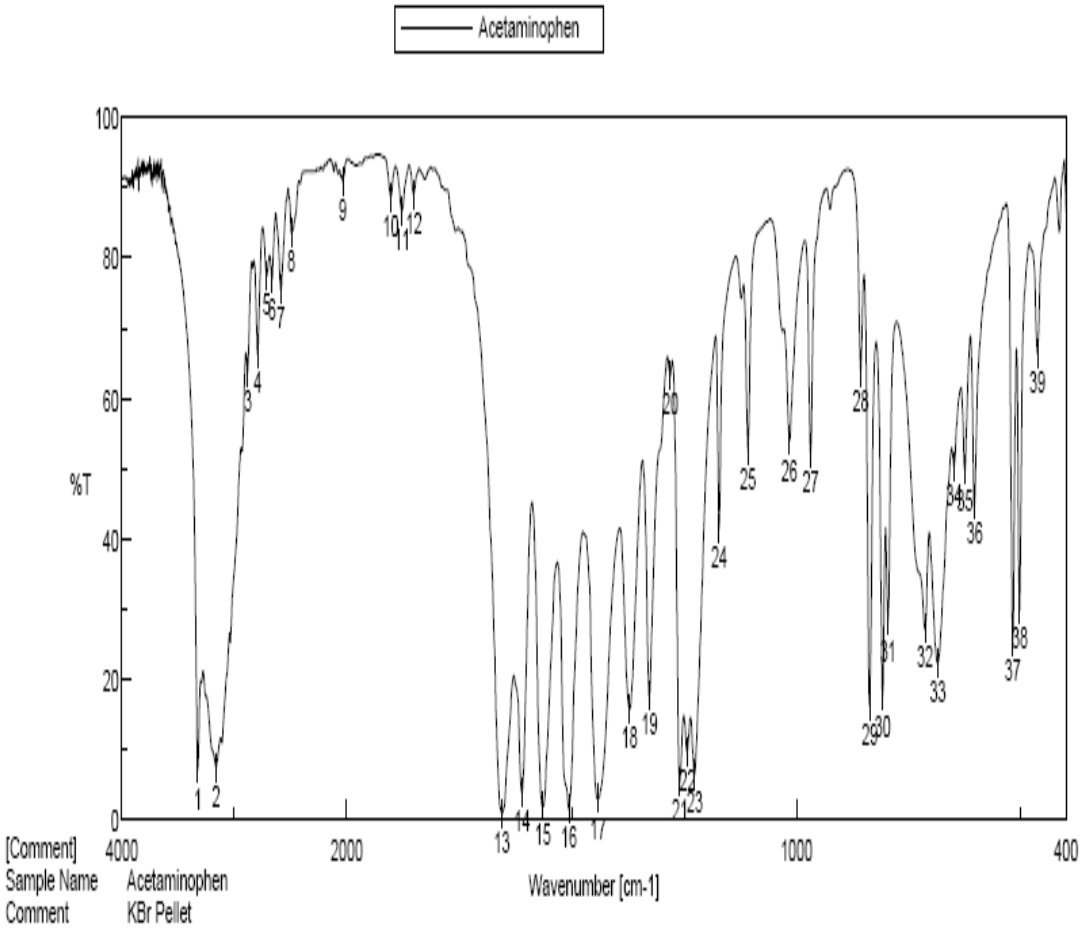
Where,

A= Acetaminophen

RH= Relative humidity

Nd = change not detectable

Figure No: 5 IR Spectra of Acetaminophen



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Sample Name	Acetaminophen
Comment	KBr Pellet
User	GMR
Division	QC

[Data Information]

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Horizontal	Wavenumber [cm-1]
Vertical	%T
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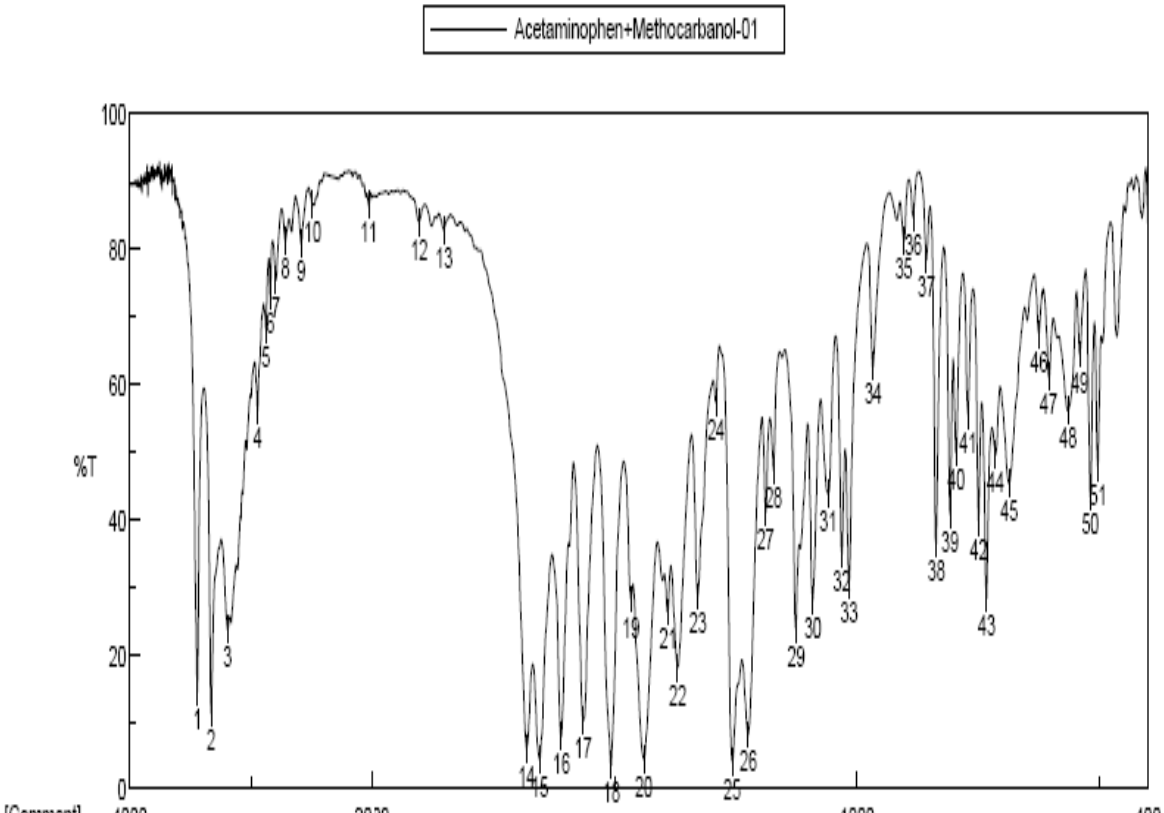
End	7800.65 cm-1
Data pitch	0.964233 cm-1
Data points	7677

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3326	7.16818	2	3162	7.37089	3	2882	63.768	4	2793	66.336
5	2713	77.3561	6	2666	76.7842	7	2586	75.3827	8	2493	83.5812
9	2035	90.8548	10	1902	86.6839	11	1877	86.6518	12	1851	89.0105
13	1655	0.841152	14	1610	3.81916	15	1564	1.85404	16	1506	1.40426
17	1442	2.87056	18	1371	15.6169	19	1327	17.5222	20	1281	63.1223
21	1259	5.24954	22	1243	9.61972	23	1227	6.56705	24	1172	41.5012
25	1108	52.6538	26	1015	53.8654	27	968	52.265	28	857	63.8072
29	837	16.1345	30	808	17.4118	31	796	28.137	32	714	27.0605
33	686	22.2388	34	649	50.1864	35	626	49.6622	36	604	44.8481
37	519	25.1387	38	503	29.823	39	464	66.439			

Figure No: 6 IR Spectra of Acetaminophen and Methocarbamol



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Comment KBr Pellet
User GMR
Division QC

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Vertical %T
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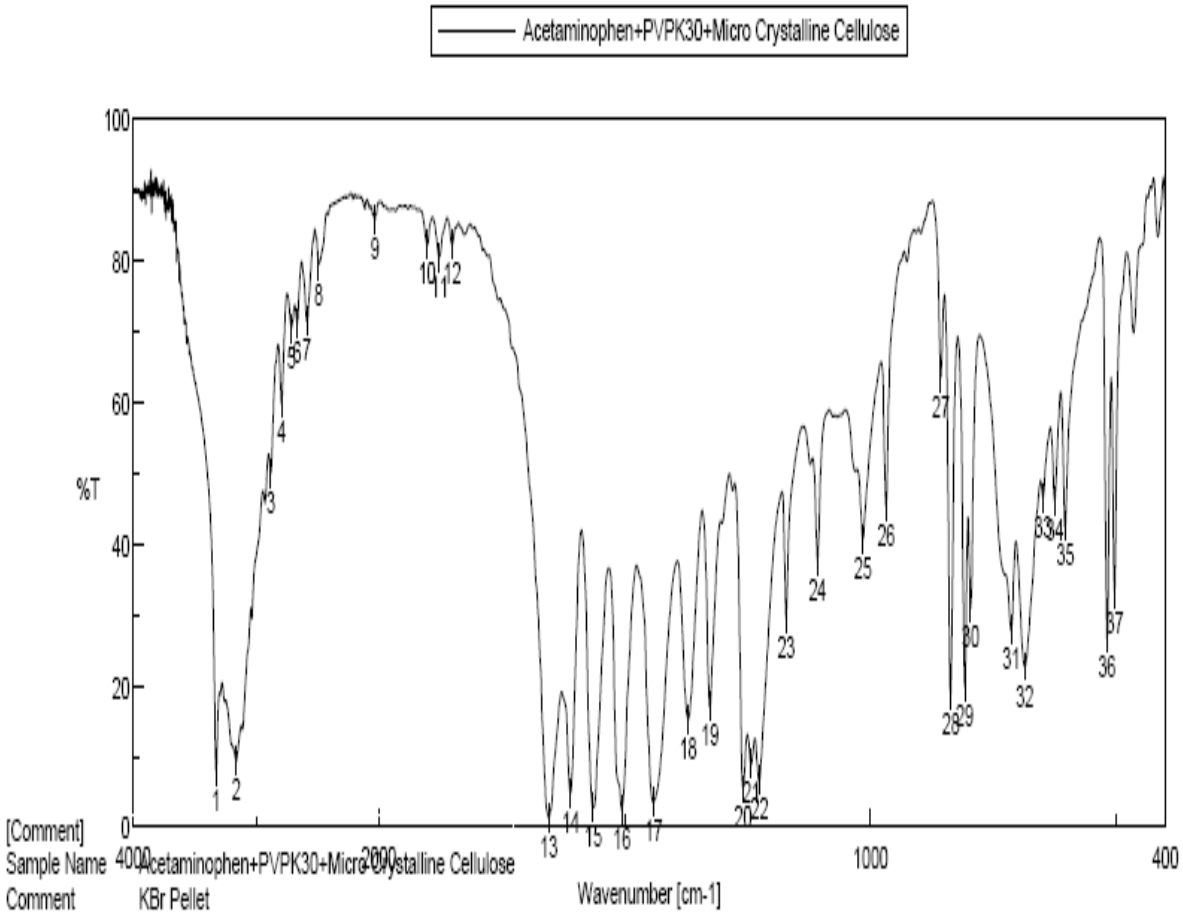
End7800.65 cm-1
Data pitch 0.964233 cm-1
Data points 7677

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3442	14.3212	2	3328	11.2693	3	3192	23.5806	4	2945	56.0191
5	2876	68.1546	6	2841	73.2088	7	2794	75.4153	8	2716	81.2016
9	2585	80.8363	10	2493	86.4214	11	2028	86.4633	12	1903	84.0495
13	1852	82.8723	14	1682	5.97404	15	1655	4.40263	16	1610	7.75774
17	1565	10.1759	18	1507	3.53942	19	1467	28.0441	20	1440	4.44517
21	1390	26.2127	22	1370	17.9884	23	1329	28.5143	24	1291	57.2883
25	1257	4.12721	26	1225	8.02392	27	1189	41.0193	28	1173	47.3514
29	1126	23.8015	30	1092	27.9002	31	1060	43.7949	32	1032	34.7347
33	1016	30.1522	34	967	62.5502	35	903	81.2319	36	884	84.7651
37	857	78.3758	38	837	36.3252	39	808	40.7404	40	795	49.8404
41	771	55.4334	42	749	39.5468	43	733	28.3289	44	714	49.5678
45	687	45.2922	46	625	67.3565	47	605	60.9414	48	565	56.0697
49	541	64.4025	50	519	43.2207	51	503	47.508			

Figure No: 7 IR Spectra of Acetaminophen ,PVP K-30 and Microcrystalline cellulose



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Comment KBr Pellet
User GMR
Division QC

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Vertical %T
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End7800.65 cm-1
Data pitch 0.964233 cm-1
Data points 7677

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3326	7.89084	2	3162	9.22829	3	2881	50.0112	4	2793	59.815
5	2714	70.4869	6	2666	71.1943	7	2586	71.4757	8	2493	79.4831
9	2034	85.842 10	1902	82.2495	11 1877	80.5517	12	1851	82.2803		
13	1655	1.35339	14	1610	4.85972	15	1564	2.80006	16	1506	2.28399
17	1442	3.54044	18	1371	15.2006	19	1327	16.9052	20	1259	5.27035
21	1243	8.78107	22	1227	6.47339	23	1172	29.4946	24	1108	37.7184
25	1015	40.695 26	968	45.418	27 857	63.6315	28	837	18.7202		
29	808	19.9069	30	796	30.8438	31	714	27.735	32	687	22.6903
33	649	46.4157	34	625	46.0425	35	604	42.3791	36	519	26.531
37	503	32.7715									

Inference: The IR spectra of pure drug Acetaminophen and physical mixture with other excipients were compared and are found to be compatable with each other as indicated by no significant change in the drug peaks.

Table No: 52 Compatibility Studies of Methocarbamol With Excipients.

Drug	Excipients (Ratio= 1:1)	1st day	1st week	2nd week	3rd week
		40^0C & 75% RH	40^0C & 75% RH	40^0C & 75% RH	40^0C & 75% RH
M	Acetaminophen	Nd	Nd	Nd	Nd
M	Pregelatinized starch	Nd	Nd	Nd	Nd
M	Micro crystalline cellulose	Nd	Nd	Nd	Nd
M	PVP K-30	Nd	Nd	Nd	Nd
M	Sodium Lauryl sulphate	Nd	Nd	Nd	Nd
M	Sodium Starch Glycolate	Nd	Nd	Nd	Nd
M	Colloidal Silicon di oxide	Nd	Nd	Nd	Nd

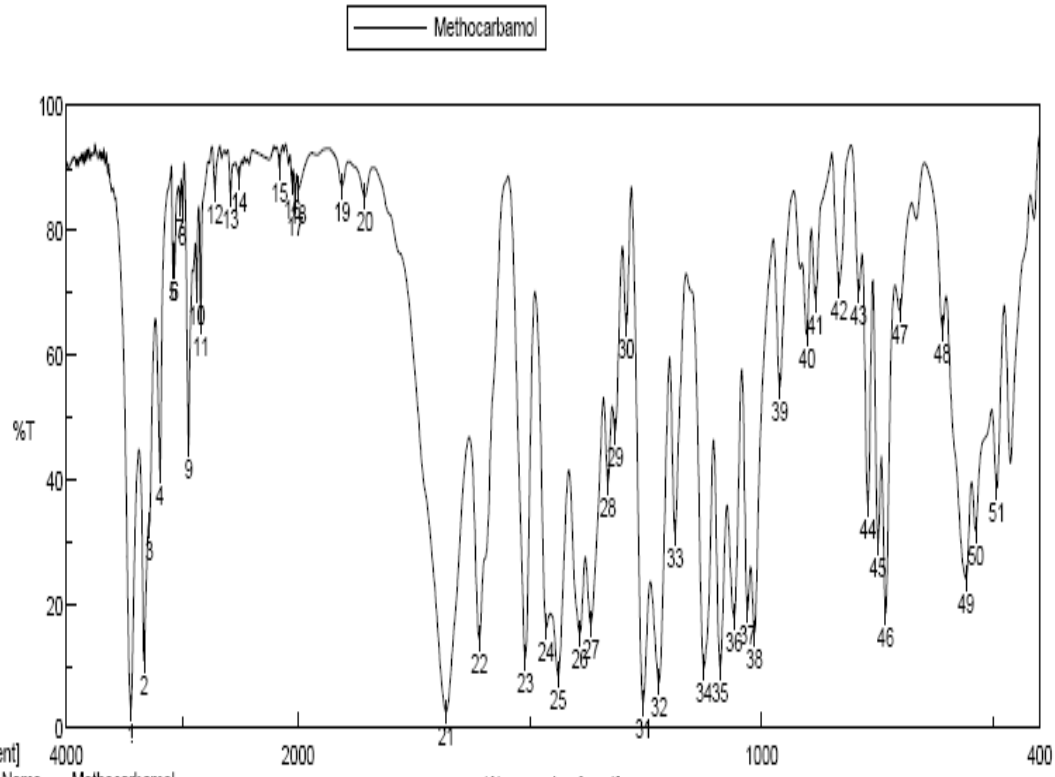
Where,

M= Methocarbamol

RH= Relative humidity

Nd = change not detectable

Figure No: 8 IR Spectra of Methocarbamol



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Comment KBr Pellet
User BKR
Division QC

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Vertical %T
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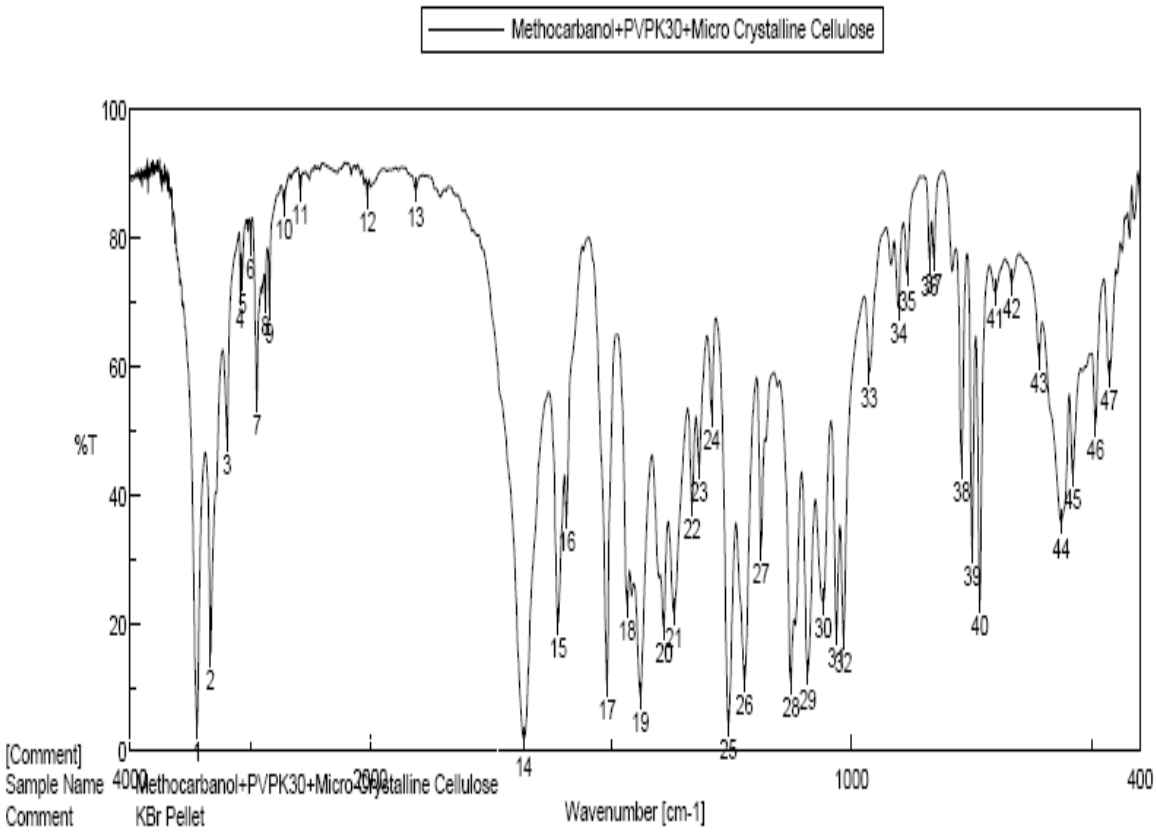
End7800.65 cm-1
Data pitch 0.964233 cm-1
Data points 7677

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3442	3.09657	2	3329	10.8723	3	3284	32.6403	4	3193	41.3264
5	3081	74.3151	6	3066	74.1848	7	3020	84.3608	8	2998	83.2759
9	2945	45.5202	10	2875	70.5033	11	2841	65.2991	12	2719	86.4556
13	2583	85.9774	14	2508	88.4147	15	2162	90.0852	16	2053	87.578
17	2027	84.7011	18	2001	86.56	19	1905	87.1268	20	1856	85.3717
21	1681	2.65027	22	1609	14.3036	23	1510	11.3262	24	1465	16.2267
25	1439	8.51117	26	1392	15.2046	27	1368	16.7477	28	1332	39.3705
29	1316	47.7246	30	1292	64.8074	31	1255	4.11484	32	1222	7.37367
33	1187	31.4403	34	1124	9.74859	35	1090	9.7789	36	1060	17.838
37	1031	18.838	38	1015	15.218	39	961	54.8332	40	903	63.2547
41	884	69.0463	42	833	71.1919	43	791	70.1981	44	770	36.012
45	749	29.7006	46	733	18.4792	47	702	67.0757	48	610	64.2947
49	559	23.9401	50	536	31.7431	51	493	38.571			

Figure No: 9 IR Spectra of Methocarbamol, PVP K-30 and Microcrystalline cellulose



Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3442	3.80733	2	3330	15.1385	3	3193	48.8456	4	3082	71.5927
5	3067	73.7897	6	2997	79.3213	7	2945	54.8089	8	2875	70.5071
9	2841	69.0639	10	2719	85.3846	11	2584	87.7339	12	2027	86.7867
13	1906	87.57	14	1682	1.81806	15	1610	20.057	16	1592	36.8064
17	1508	10.6344	18	1467	22.8236	19	1439	8.75175	20	1390	19.4566
21	1369	21.6921	22	1332	38.4963	23	1317	44.6344	24	1291	52.6203
25	1256	4.37684	26	1223	11.2393	27	1188	31.8249	28	1126	10.8946
29	1092	12.2053	30	1059	23.3285	31	1032	18.6919	32	1017	17.7889
33	963	59.176	34	903	69.1839	35	884	74.3846	36	838	76.6853
37	829	76.8991	38	771	44.6186	39	749	31.3441	40	734	23.6192
41	702	71.6376	42	667	73.0095	43	610	61.4985	44	564	35.7601
45	540	43.3783	46	493	51.0836	47	465	58.7731			

Inference: The IR spectra of pure drug Methocarbamol and physical mixture with other excipients were compared and are found to be compatable with each other as indicated by no significant change in the drug peaks between pure drug sample and drug excipient physical mixture.

7.3 PRE COMPRESSION PARAMETER:

Table No: 53 Precompression Parameter of Acetaminophen Granules Trials:

Formulations	Bulk density (gm/cm^2)	Tapped density (gm/cm^2)	C.I (%)	Angle of repose (^{0})	H.R	Moisture Content
F1	0.44	0.55	27.0	50°.12’	1.44	0.681
F2	0.41	0.51	28.33	47°.32’	1.42	0.630
F3	0.43	0.52	27.3	48°.26’	1.382	0.612
F4	0.41	0.51	29.61	46°.56’	1.255	0.586
F5	0.42	0.54	32.22	42°.21’	1.383	0.323
F6	0.49	0.50	20.0	38°.65’	1.222	0.311
F7	0.48	0.55	18.15	36°.23’	1.25	0.262
F8	0.48	0.51	15.69	28°.13’	1.146	0.216
F9	0.47	0.55	20.0	30°.23’	1.25	0.218

Inference: Formulations F1 to F5 has high angle of repose and Hausners ratio indicating poor flow of granules and the flow property increased in case of F6 and F7 because of inclusion of a dry binder and F8 and F9 has shown good flow as indicated by angle of repose and Hausners ratio because of increase in concentration of lubricant Stearic acid

Table No: 54 Precompression Parameter of Methocarbamol Granules Trials:

Formulations	Bulk density (gm/cm^2)	Tapped density (gm/cm^2)	C.I (%)	Angle of repose (^{0})	H.R	Moisture Content
F1	0.45	0.56	28.64	46°.66’	1.39	0.621
F2	0.44	0.57	31.8	48°.2’	1.38	0.627
F3	0.41	0.59	30.5	50°.56’	1.40	0.612
F4	0.44	0.57	32.8	46°.99’	1.383	0.531
F5	0.44	0.56	24.42	47°.3’	1.382	0.523
F6	0.43	0.54	20.37	42°.21’	1.255	0.322
F7	0.47	0.59	18.64	34°.56’	1.208	0.292
F8	0.48	0.58	17.24	30°.12’	1.124	0.242
F9	0.45	0.55	18.18	31°.63’	1.125	0.245

Inference: Formulation F1 to F7 has high angle of repose and Hausners ratio and the values reduced by addition of increasing concentration of Sodium lauryl sulphate as lubricant that enhanced flow property.

7.4 POST COMPRESSION PARAMETER OF ACETAMINOPHEN AND METHOCARBAMOL TABLETS:

Table No: 55 Post Compression Parameter of Acetaminophen and Methocarbamol Tablets.

Formulations	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration time (min)	Friability (%)
F1	1025-1033	17.1	6.72	16	0.008
F2	1020-1030	16.8	6.66	12	0.068
F3	1015-1032	8.9	6.74	6	1.062
F4	1032-1038	9.1	6.84	8	1.076
F5	1004-1034	11.1	6.63	7	0.089
F6	1036-1045	14.3	6.88	4	1.174
F7	1012-1024	13	6.71	5	0.041
F8	980-1040	13.7	6.75	6	0.055
F9	1032-1039	13.3	6.72	5	0.050

7.5 DRUG CONTENT:

Table No: 56 Drug Content Values of Acetaminophen and Methocarbamol

FORMULATIONS	ACETAMINOPHEN	METHOCARBAMOL
F5	98.12%	97.23%
F6	99.01%	98.25%
F7	100.02%	100.05%
F8	100.08%	100.03%
F9	100.05%	100.01%

7.6.1 INNOVATOR DRUG RELEASE PROFILE:

Table No: 57 Innovator Drug Release Profile:

TIME (MIN)	INNOVATOR (ACETAMINOPHEN)	INNOVATOR (METHOCARBAMOL)
10	72.4%	70.7%
15	84.2%	82.6%
30	93.2%	91.3%
45	96.8%	94.9%

60	98.2%	96.4%

7.6.2 DRUG RELEASE VALUES OF ACETAMINOPHEN AND METHOCARBAMOL

Table No: 58 Drug Release Values of Acetaminophen and Methocarbamol

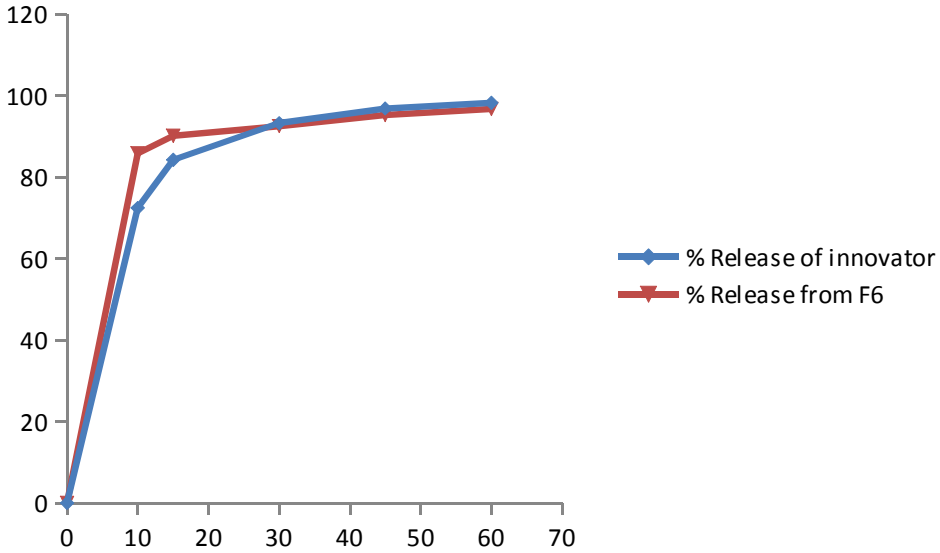
FORMULATIONS	ACETAMINOPHEN	METHOCARBAMOL
F5	95.8%	95.6%
F6	96.7%	90.2%
F7	96.6%	96.6%
F8	97.8%	97.2%
F9	96.1%	97.1%

7.6.3(A) RELEASE PROFILE OF ACETAMINOPHEN IN F6 COMPARED WITH INNOVATOR

Table No: 59 Comparitive release of Acetaminophen from innovator and F6

Time(min)	% Release of innovator	% Release from F6
10	72.4	85.8
15	84.2	90.1
30	93.2	92.5
45	96.8	95.2
60	98.2	96.7

Figure No: 10 Comparitive release of Acetaminophen from innovator and F6



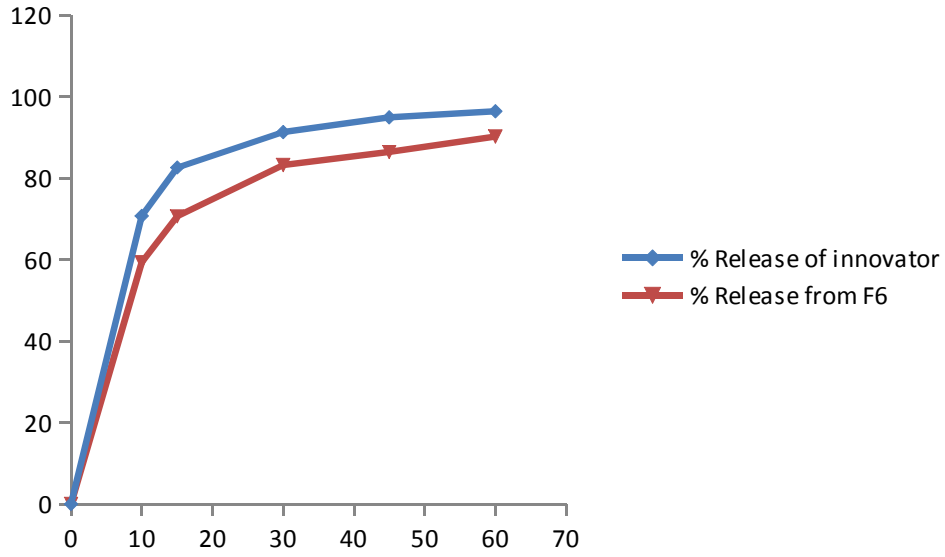
Inference: The Release profile of Acetaminophen from F6 was compared to innovator initially more release and then the release was less than inovator at the end of 45 and 60min

7.6.3(B) COMPARITIVE RELEASE OF METHOCARBAMOL FROM INNOVATOR AND F6

Table No: 60 Comparitive release of Methocarbamol from innovator and F6

Time(min)	% Release of innovator	% Release from F8
10	70.7	59.3
15	82.6	70.6
30	91.3	83.2
45	94.9	86.4
60	96.4	90.2

Figure No: 11 Comparitive release of Methocarbamol from innovator and F6



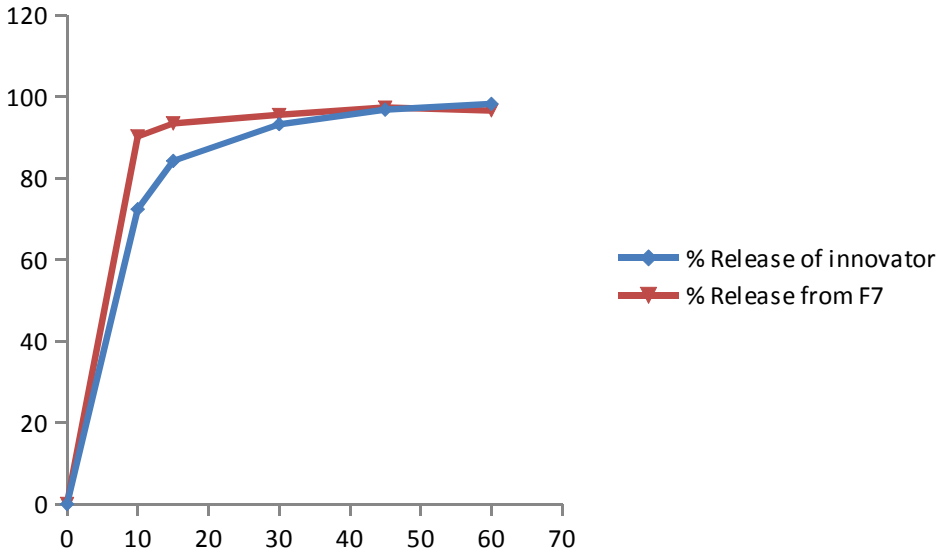
Inference: The Release profile of Methocarbamol from F6 was compared to innovator and the release rate was less than inovator at the end of 45 and 60min.

7.6.4(A) RELEASE PROFILE OF ACETAMINOPHEN IN F7 COMPARED WITH INNOVATOR

Table No: 61 Comparitive release of Acetaminophen from innovator and F7

Time(min)	% Release of innovator	% Release from F7
10	72.4	90.2
15	84.2	93.4
30	93.2	95.5
45	96.8	97.3
60	98.2	96.6

Figure No: 12 Comparitive release of Acetaminophen from innovator and F7



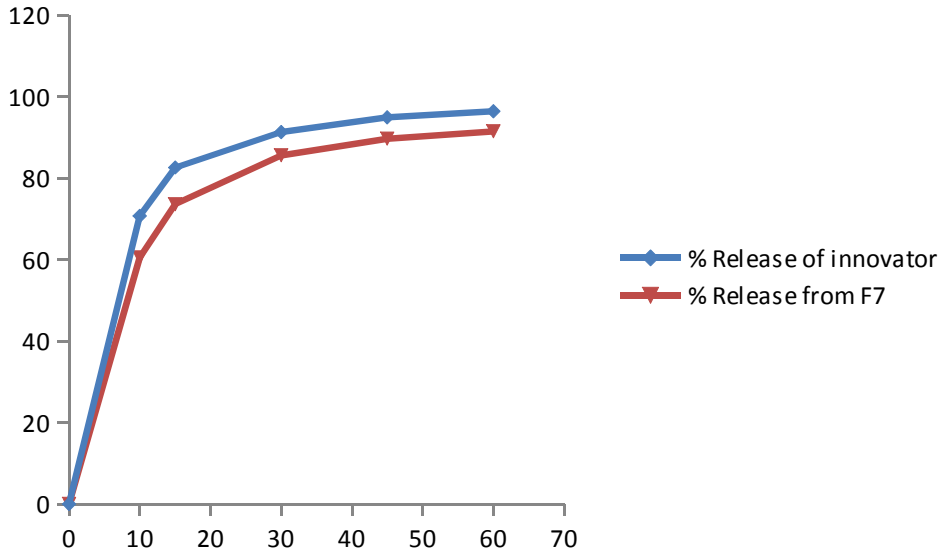
Inference: The Release profile of Acetaminophen from F7 was more compared to innovator initially and the release was less than inovator at the end of 45 and 60min.

7.6.4(B) COMPARITIVE RELEASE OF METHOCARBAMOL FROM INNOVATOR AND F7

Table No: 62 Comparitive release of Methocarbamol from innovator and F7

Time(min)	% Release of innovator	% Release from F7
10	70.7	60.5
15	82.6	73.6
30	91.3	85.6
45	94.9	89.7
60	96.4	91.5

Figure No: 13 Comparitive release of Methocarbamol from innovator and F7



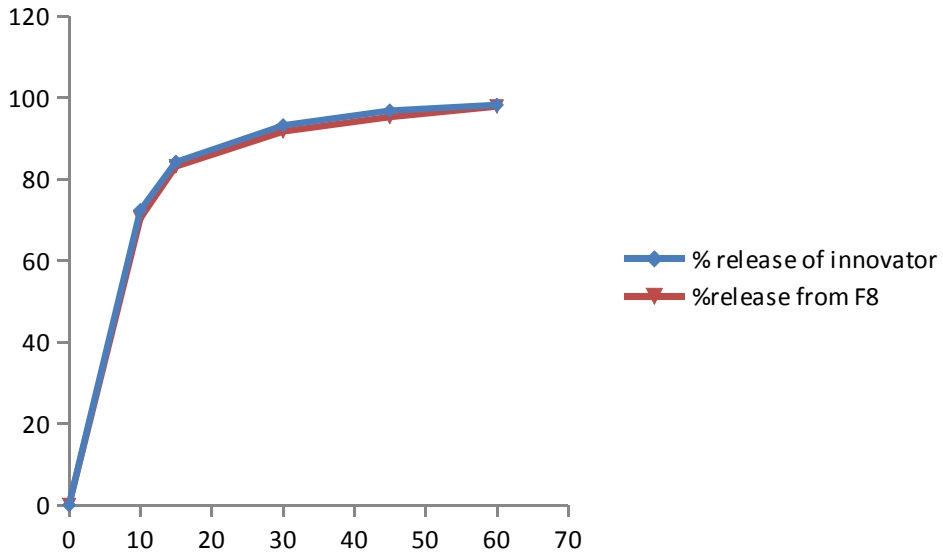
Inference: The Release profile of Methocarbamol from F7 was compared to innovator and the release rate was less than inovator at the end of 45 and 60min.

7.6.5(A) COMPARITIVE RELEASE OF ACETAMINOPHEN FROM INNOVATOR AND F8

Table No: 63 Comparitive release of Acetaminophen from innovator and F8

Time(min)	% Release of innovator	% Release from F8
10	72.4	70.4
15	84.2	83.1
30	93.2	91.7
45	96.8	95.2
60	98.2	97.8

Figure No: 14 Comparitive release of Acetaminophen from innovator and F8



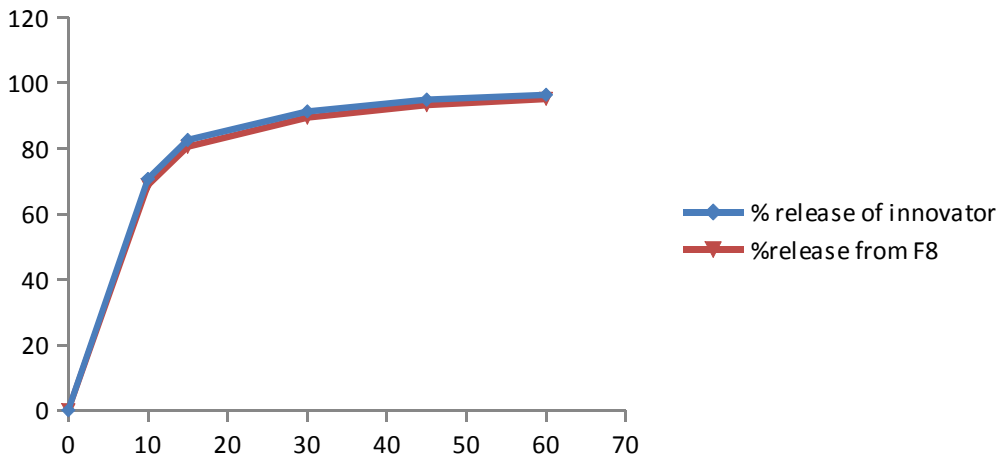
Inference: The Release profile of Acetaminophen from F8 was compared to innovator and the release was almost equal and comparable to that of inovator at the end of 45 and 60min.

7.6.5(B) COMPARITIVE RELEASE OF METHOCARBAMOL FROM INNOVATOR AND F8

Table No: 64 Comparitive release of Methocarbamol from innovator and F8

Time(min)	% Release of innovator	% Release from F8
10	70.7	68.7
15	82.6	80.5
30	91.3	89.4
45	94.9	93.2
60	96.4	95.1

Figure No: 15 Comparitive release of Methocarbamol from innovator and F8



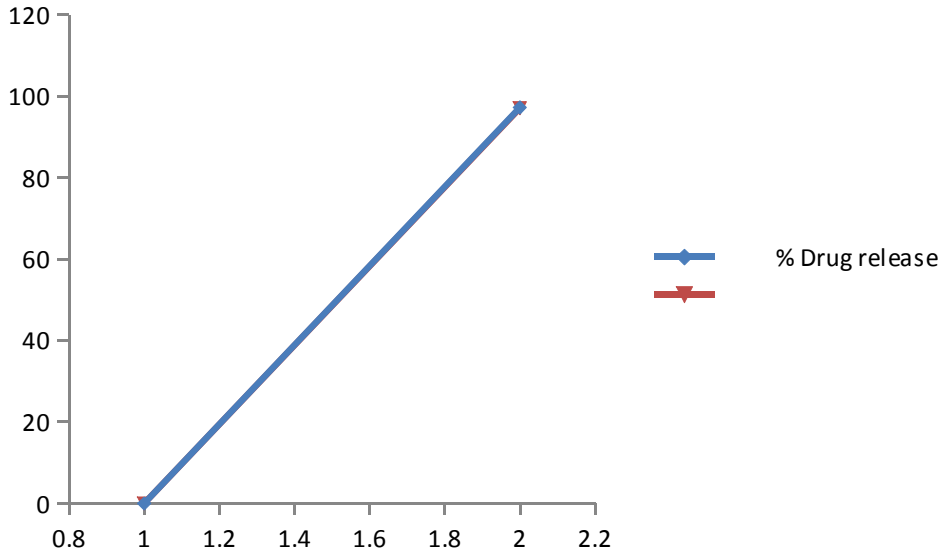
Inference: The Release profile of Methocarbamol from F8 was compared to innovator and the release was almost equal and comparable to that of inovator at the end of 45 and 60min.

7.6.6(A) RELEASE PROFILE OF ACETAMINOPHEN IN F9 COMPARED WITH INNOVATOR

Table No: 65 Comparitive release of Acetaminophen from innovator and F9

Time(min)	% Release of innovator	% Release from F9
10	72.4	70.1
15	84.2	81.9
30	93.2	91.2
45	96.8	94.8
60	98.2	97.0

Figure No: 16 Release profile of Acetaminophen in F9 compared with innovator



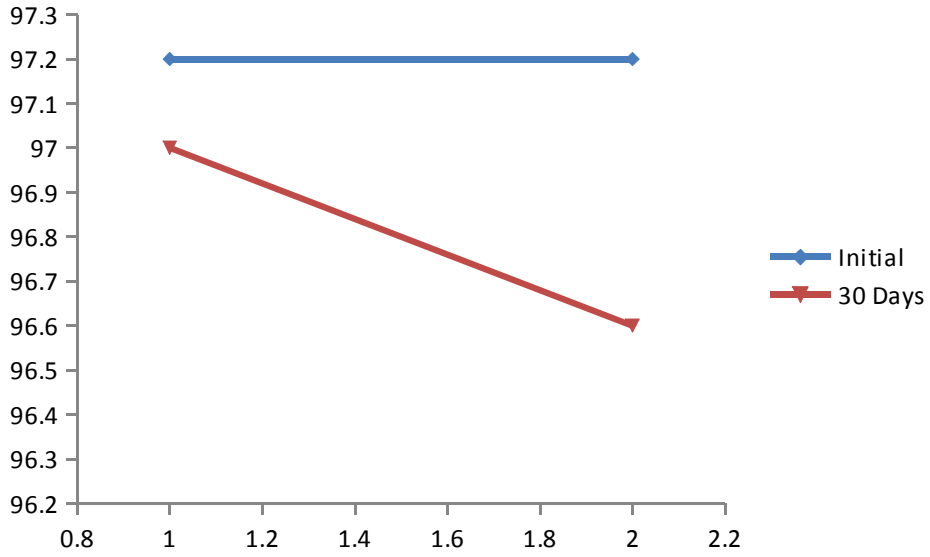
Inference: The Release profile of Acetaminophen from F9 was compared to innovator and the release was less than that of inovator.

7.6.6(B) COMPARITIVE RELEASE OF METHOCARBAMOL FROM INNOVATOR AND F9

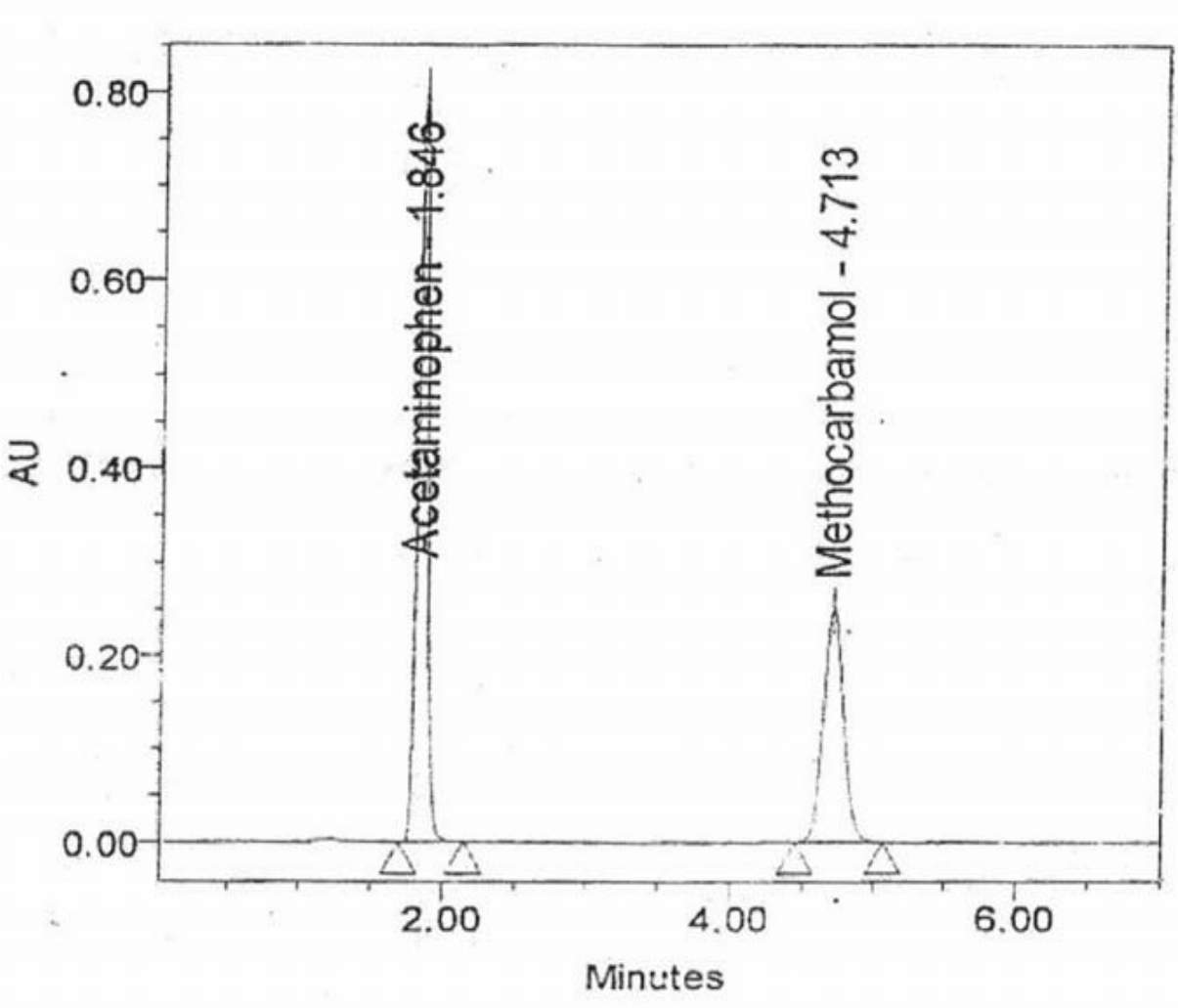
Table No: 66 Comparitive release of Methocarbamol from innovator and F9

Time(min)	% Release of innovator	% Release from F9
10	70.7	68.2
15	82.6	80.1
30	91.3	89.1
45	94.9	93.0
60	96.4	94.5

Figure No: 17 Comparitive release of Methocarbamol from innovator and F9



Inference: The Release profile of Methocarbamol from F9 was compared to innovator and the release was less than that of inovator.



Inference: HPLC Chromatogram showing peaks of Acetaminophen and Methocarbamol release from formulation F8.

7.6.7 COMPARISON OF DISSOLUTION PROFILE OF FORMULATIONS WITH INNOVATOR

Table No: 67 Comparison of dissolution profile of formulations with innovator

Time (min)	Innovator (A)	Innovator (M)	% Drug Release							
			A	**M**	**A**	**M**	**A**	**M**	**A**	**M**
			F6	**F6**	**F7**	**F7**	**F8**	**F8**	**F9**	**F9**
10	72.4	70.7	85.8	59.3	90.2	60.5	**70.4**	**68.7**	70.1	68.2
15	84.2	82.6	90.1	70.6	93.4	73.6	**83.1**	**80.5**	81.9	80.1
30	93.2	91.3	92.5	83.2	95.5	85.6	**91.7**	**89.4**	91.2	89.1
45	96.8	94.9	95.2	86.4	97.3	89.7	**95.2**	**93.2**	94.8	93.0
60	98.2	96.4	96.7	90.2	96.6	91.5	**97.2**	**95.8**	97.0	95.4

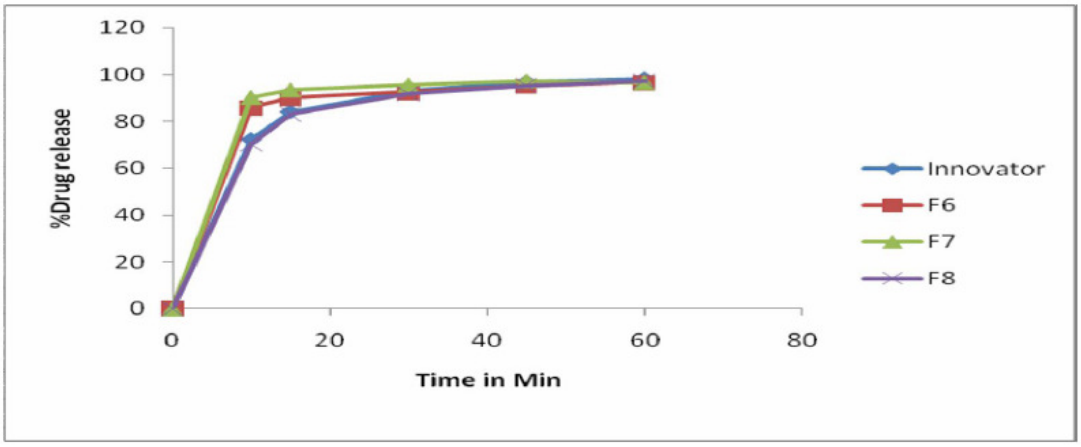
Where,

A = Acetaminophen

M = Methocarbamol

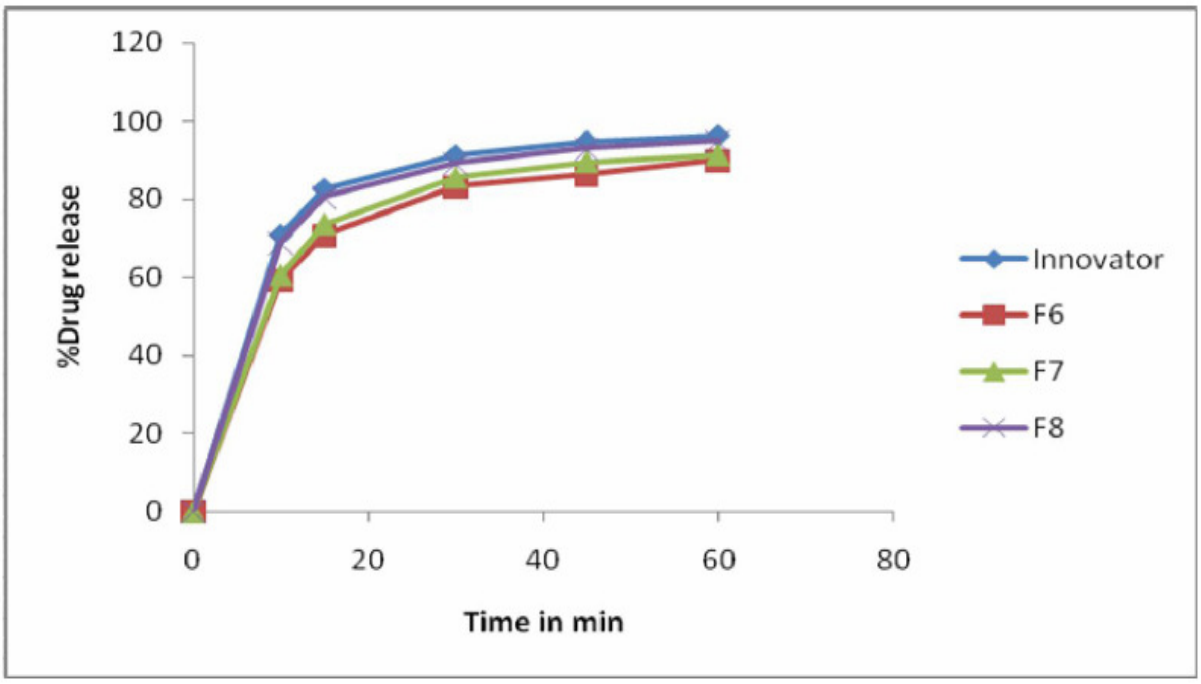
7.6.8 COMPARATIVE RELEASE PROFILE OF ACETAMINOPHEN IN VARIOUS FORMULATION WITH INNOVATOR

Figure No: 18 Comparative release profile of Acetaminophen in various formulation with innovator



Inference: Comparative release profile of Acetaminophen from various formulations showing that the release from formulation F8 matching with that of inovator

Figure No: 19 Methocarbamol release from various formulations compared to innovator



Inference: Comparative release profile of Methocarbamol from various formulations showing that the release from formulation F8 matching with that of innovator.

7.7 STABILITY STUDY

7.7.1 STABILITY DATAS FOR OPTIMIZED FORMULATIONS AT 25°C & 60% RH FOR ACETAMINOPHEN AND METHOCARBAMOL BILAYER TABLETS

Table No: 68 Stability Datas for Optimized Formulations at 25°C & 60 % RH for Acetaminophen and Methocarbamol Bilayer tablets

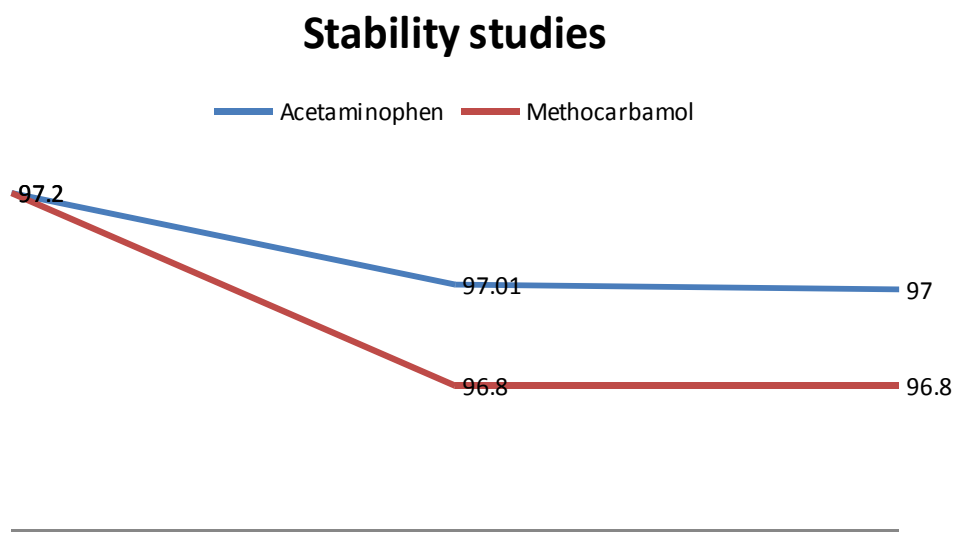
S.NO	PARAMETERS	STORAGE CONDITION (25°C & 60% RH)		
		INITIAL	30DAYS	45DAYS
1	Description	White and Green Coloured, Caplet Shaped	N.D	N.D
2	Weight Variation	980-1040	Within limits	Within limits
3	Hardness (kg/cm^2)	13.7	13.5	13.3
4	Thickness (mm)	6.75	6.75	6.75
5	Friability (%)	0.055	0.058	0.060
6	Disintegration Time (mins)	6	7	7
7	Drug Content (%) (Acetaminophen)	100.08	100.05	100.02
8	Drug Content (%) (Methocarbamol)	100.03	100.01	99.96
9	Drug Release (%) (acetaminophen)	97.2%	97.01%	97.0%
10	Drug Release (%) (Methocarbamol)	97.2%	96.8%	96.8%
11	Moisture Content	0.216	0.219	0.321

Table No: 69 Drug release of acetaminophen and methocarbamol at 25°C & 60%RH

Drug	% Drug release		
	Initial	30 Days	45 Days
Acetaminophen	97.2	97.01	97.0

Methocarbamol	97.2	96.8	96.8

Figure No: 20 Drug release of acetaminophen and methocarbamol at 25°C & 60%RH



Inference: The drug release was not significantly reduced at the end of 30days and 45days storage at 25°C & 60%RH indicating stability of the formulation. All the parameters are with in the limits specified at the end of storage period.

7.7.2 STABILITY DATAS FOR OPTIMIZED FORMULATIONS AT 40°C & 75% RH FOR ACETAMINOPHEN AND METHOCARBAMOL BILAYER TABLETS

Table No: 70 Stability Datas for Optimized Formulations at 40°c & 75 % RH for Acetaminophen and Methocarbamol Bilayer tablets

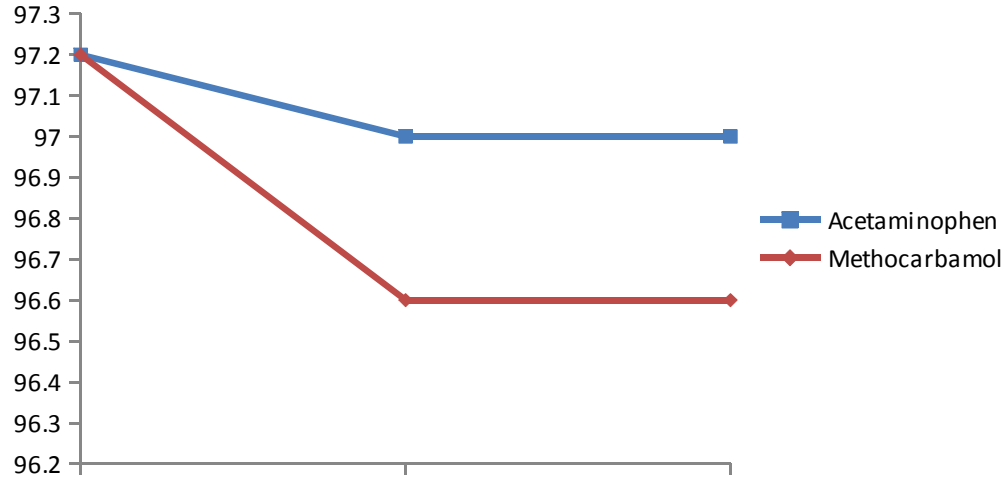
S.NO	PARAMETERS	STORAGE CONDITION (40°C & 75% RH)

		INITIAL	30DAYS	45DAYS
1	Description	White and Green Coloured, Caplet Shaped	N.D	N.D
2	Weight Variation	980-1040	980-1040	980-1040
3	Hardness (kg/cm^2)	13.7	Within limits	Within limits
4	Thickness (mm)	6.75	6.75	6.75
5	Friability (%)	0.055	0.062	0.064
6	Disintegration Time (mins)	6	7	7
7	Drug Content (%) (Acetaminophen)	100.08	100.03	100.0
8	Drug Content (%) (Methocarbamol)	100.03	99.96	99.94
9	Drug Release (%) (acetaminophen)	97.2%	97.0%	97.0%
10	Drug Release (%) (Methocarbamol)	97.2%	96.6%	96.6%
11	Moisture Content	0.216	0.227	0.231

Table No: 71 Drug release of Acetaminophen and Methocarbamol at 40^{o}C & 75%RH

Drug	% Drug release		
	Initial	30 Days	45 Days
Acetaminophen	97.2	97.0	97.0
Methocarbamol	97.2	96.6	96.6

Figure No: 21 Drug release of Acetaminophen and Methocarbamol at 40ºC & 75%RH



Inference: The drug release was not significantly reduced at the end of 30days and 45days storage at 40ºC & 75%RH indicating stability of the formulation. All the parameters are with in the limits specified at the end of storage period.

8. SUMMARY AND CONCLUSION

The present study was aimed at developing a bilayer tablet of Acetaminophen and Methocarbamol.

Totally 9 formulations are prepared with Acetaminophen and Methocarbamol granules prepared separately in a rapid mixer granules.

Pre compression parameters like Bulk density, True density, Angle of repose indicate all the formulations are showing good flow properties.

Tablets are compressed using SEJONG bilayer compression machine and tablets are evaluated for post compression parameters Weight variation, Hardness, Friability, Disintegration and Dissolution parameters.

Formulations F1-F4 does not meet the direct criteria for Hardness and Disintegration time due to improper mixing of binder with the dry mixture.

Formulations F5-F9 has shown post compression parameters within the specified limits of the innovator. The release profile of formulations F5-F9 was compared with innovator and all the formulations has shown a release of 70-95% and formulation F8 has matched the innovator release profile.

The compressed belayer tablets was packed in blisters and subjected to stability studies at 40°C and 75% RH, 25°C and 60% RH. Samples were analyzed at regular intervals as mentioned in stability protocol.

From the study, it may be concluded that bilayer tablet of Acetaminophen and Methocarbamol can be prepared as immediate release formulation compared to conventional formulations.

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