CHAPTER 4

FORMULATION DEVELOPMENT (BUTORPHANOL TARTRATE)

4.0 Formulation Development (Butorphanol Tartrate)

The main objective of the present work is to develop extended release solid oral formulation of Butorphanol Tartrate (BT) for maintaining therapeutic blood levels of the drug for extended period of time and improve patient compliance by minimizing local and systemic adverse effect. Table 1-4 lists the equipment used for development.

Sr. No.	Instruments	Make
1.	Compression	8-station compression machine, KMP-8, Cadmach Engg, Ahmedabad, India.
2.	Coating	Perforated pan, Solace Autocoater, India.
3.	Digital weighing balance	AG-64, Mettler Toledo, Switzerland
4.	Tap density tester	ETD-1020, Electrolab, Mumbai, India.
5.	Hardness tester	6-D, Dr Schleuniger Pharmatron, Manchester, NH, USA
6.	pH meter	Mettler Toledo, Switzerland
7.	Tray dryer	Bombay Eng. Works, Mumbai, India
8.	Friability tester	EF-2, Electrolab, Mumbai, India
9.	Thickness gauge	Digimatic Caliper, Mitutoyo, Japan
10.	Bath sonicator	DTC 503, Ultra Sonics, Vetra, Italy
11.	Stability chamber	Thermolab, Mumbai, India
12.	Differential Scanning Calorimeter (DSC)	Mettler DSC 20, Mettler Toledo, Switzerland
13.	Scanning electron microscope (SEM)	JSM-6360, Jeol, Japan
14.	Stability oven	Shree Kailash Industries, Vadodara
15.	HPLC system	LC 20-AT prominence, Shimadzu Corp., Japan
16.	UV-Visible Spectrophotometer	Shimadzu UV-1601, Japan

17.	Nuclepore Polycarbonate membrane 2 µm 25mm	Whatman, USA

Table 1 - 4 Equipments Used

4.1 Drug Substance

Butorphanol Tartrate

The drug substance attribute, affects the drug product development, manufacture, performance and stability. The following aspects were considered during the product development:

Physiochemical properties of Drug

As physicochemical drug properties plays an important role in the manufacturing of a dosage form and its therapeutic activity, the characterization of the powder properties of Butorphanol Tartrate among all the physicochemical properties was found to be important.

Particle size distribution of drug substance: Butorphanol Tartrate water soluble drug, particle size would not have significant impact on the rate of dissolution of drug and hence on the bioavailability

Bulk density and tapped density: Concentration of the drug in the formulation is less 5% w/w so density of the formulation is not going to be affected majorly by density of drug.

The stability of the Butorphanol tartrate is not affected by aqueous media and hence wet granulation method was adopted for the product development. Stability of the Butorphanol tartrate is not affected by aqueous media and hence wet granulation method was adopted for the product development. Butorphanol tartrate is not light sensitive and hence processing was done under normal light. Commonly used excipients were employed for development of tablet dosage form of Butorphanol tartrate.

Partition Coefficient: The n-octanol/aqueous buffer partition coefficient of butorphanol is 180:1 at pH 7.5. (34th ECDD 2006/4.1)

Physical Description: A white or almost white crystalline powder

Melting Point: It melts at 217°C to 219°C. (34th ECDD 2006/4.1)

Stability: Butorphanol Tartrate is very stable compound no individual degradation products were identified during forced degradation studies.

Biopharmaceutical Classification System (BCS) category: BCS has categorized Butorphanol Tartrate in Class I, i.e. High solubility High permeability.

4.2 Pharmacokinetics

Butorphanol is rapidly absorbed, widely distributed, undergoes extensive hepatic first-pass metabolism, and is excreted primarily via the kidneys. (34th ECDD 2006/4.1)

Peak plasma concentrations of 2.2 ng/mL butorphanol occur between 30-60 min after a single 2-mg i.m. administration. Peak plasma concentrations of 1.5 ng/mL butorphanol occur almost immediately after a single 1-mg i.v. administration. Apparent plasma half-life of butorphanol is between 6 and 10 h. (Boulton et al., 2002)

Butorphanol exhibits partial agonist and antagonist activity at the μ opioid receptor and agonist activity at the κ opioid receptor. Stimulation of these receptors on central nervous system neurons causes an intracellular inhibition of adenylate cyclase, closing of influx membrane calcium channels, and opening of membrane potassium channels. This leads to hyperpolarization of the cell membrane potential and suppression of action potential transmission of ascending pain pathways. Because of its κ-agonist activity, at analgesic doses butorphanol increases pulmonary arterial pressure and cardiac work. Additionally, κ-agonism can cause dysphoria at therapeutic or supertherapeutic doses; this gives butorphanol a lower potential for abuse than other opioid drugs. (Wikipedia)

Oral absorption of Butorphanol (Tartrate) is found to be 70% ±20. Volume of distribution is found to be 12l/kg and plasma protien binding is 80% and metabolism is reported Hepatic. Renal Excretion accounts for 1.05% and plasma half life is 2.5 - 4 hr. (http://druginfosys.com 17th March 2011) Peak plasma concentration of 0.7 ng/ml was achieved 1 to 1.5 hr following the 8 mg of oral dose.

Butorphanol is completely absorbed form gastro-intestinal track and following intra- muscular injection.

After intramuscular or intravenous administration, butorphanol is widely distributed to tissues with an estimated volume of distribution ranging from 300-900 mL. The extent of plasma protein binding is approximately 80%. (Gaver et al.,1980).

Butorphanol rapidly crosses the placenta and neonatal serum concentrations are 0.4-1.4 times maternal concentrations. Butorphanol is distributed into breast milk although breastfed infants would receive a negligible amount. Doses of 8 mg intramuscular to 12 healthy nursing mothers resulted in neonatal exposure of only 4 mcg. (Pittman et al., 1980a; Pittman et al., 1980b)

Following oral administration mean oral bioavailability of unchanged butorphanol is 17% due to hepatic first-pass metabolism. Due to the extensive hepatic metabolism of butorphanol, oral bioavailability is approximately 5 to 17%. Sublingual tablet and buccal disk formulations only increased mean absolute bioavailability to 19 and 29%. Butorphanol is metabolized by hydroxylation and N-dealkylation to form the major metabolite hydroxybutorphanol (45-50% of parenterally administered dose) and norbutorphanol (5-10% of parenterally administered dose). (Vachharajani et al., 1997a; Vachharajani et al., 1997b). Neither metabolite appears to have any pharmacological effects. (Gaver et al.,1980).

The major route of elimination for Butorphanol and its metabolite is renal. Less than 5% of butorphnol is excreted unchanged in urine, and principal urinary metabolite being free hydroxybutorphanol.

4.3 Pharmacodynamic Properties

Butorphanol (Tartrate) is opioid analgesic. Butorphanol (Tartrate) is used to relieve the pain. It has some narcotic activity. Butorphanol (Tartrate) is used to relieve pain of surgical procedures and labor and to enhance the effects of anesthesia. Long term use of butorphanol tartrate can produce dependence. (http://druginfosys.com 17th March 2011)

Studies of oral administration have demonstrated analgesic activity with doses of 4 to 16mg of butorphanol. 8 or 16mg oral doses produced a peak analgesic effect similar to that seen with 60mg of codeine when given for a few days to patients with acute musculoskeletal or episiotomy pain, but butorphanol appeared to be longer acting and was thus often statistically superior to codeine at 4 to 6 hours after administration of a dose. Similarly, a single 8mg dose of oral butorphanol was more effective than 50mg of pentazocine (usual oral dose 50 to 100mg) at several evaluation times in postoperative patients, and appeared to be longer acting. (Butorphanol 1978)

Only a small group of patients with chronic pain have received repeated intramuscular or oral doses of butorphanol over an extended period. Treatment was discontinued due to side effects (sedation, nausea, confusion, dizziness, rash) in 18 of 63 patients receiving repeated injections (usually 2 or 4mg) for up to 34 weeks. In a small number of patients who received oral treatment over a 6 to 8 month period, no drug related changes in laboratory or physical examination findings occurred. However, further studies in which larger numbers of patients are treated for

extended periods are needed to more clearly determine the drug's tolerability and safety when used in the treatment of chronic pain. (Butorphanol 1978)

Oral butorphhanol is comparable to oral midazolam in children but analgesia alongwith sedation is an additional advantage which makes it better than midazolam without a significant increase in side effects. (Singh et al., 2005)

Mechanism of Action

Butorphanol, a synthetic morphinan derivative, was developed so as to minimize side effects associated with normal narcotic analgesics. Butorphanol is a mixed agonist-antagonist with low intrinsic activity at receptors of the μ-opioid type (morphine-like). It is also an agonist at k-opioid receptors. The analgesic potency of butorphanol is approx 5 times to that of morphine, 35 times that of meperidine, 17 times that of pentazocine, and very less than that of naloxone. Butorphanol also has a strong antitussive effect that is approx 100 times that of codeine.

4.4 Excipients:

4.4.1 Excipient used in drug product:

Following table describes the list of excipients. Table 2-4 includes all raw materials used in the manufacture of the drug product, whether they appear in the finished product or not. All excipients used in fabrication of drug product matches with specifications commonly used in design of oral products.

Ingredients	Functional Category	Source
Butorphanol Tartrate	Active	Theraquest (Supplied By Teva)
Lactose Monohydrate	Osmogen	Granulac 200, Meggle.
Microcrystalline cellulose	Diluent	Celphere CP-102, AsahiKASEI, Japan
Polyvinyl Pyrrolidone	Binder	Kollidon, BASF, Germany
Mannitol	Osmogen	Pearlitol 200 SD, Roquette, France
Sodium chloride	Osmogen	S.D. Fine Chemicals Ltd, Mumbai, India
Purified Talc	Antiadherant	Luzenac
Tartaric acid	pH Modifier	S.D. Fine Chemicals Ltd, Mumbai, India
Magnesium stearate	Lubricant	Mallinckrodt, USA

Colloidal silicon dioxide	Glidant	Aerosil 200, Degussa, Frankfurt, Germany
Polyethylene Glycol 400 (Liquid form)	Plasticizer	S.D. Fine Chemicals Ltd, Mumbai, India
Sorbitol	Pore Former	Qualigens Fine Chemicals, Mumbai, India
Cellulose acetate (CA-398-10 NF)	Film Former	Eastman Chemical Inc, Kingsport, TN, USA
HPMC (Methocel Series)	Matrix Forming Agent	Colorcon Asia Pvt. Ltd, Goa, India
Polyethylene oxide (Polyox WSR Series)	Cross Linker	The Dow Chemical Company, MI, USA
Purified Water *	Processing solvent	Prepared in laboratory by distillation
Acetone *	Processing solvent	S.D. Fine Chemicals Ltd, Mumbai, India
Isopropyl Alcohol *	Processing solvent	S.D. Fine Chemicals Ltd, Mumbai, India

Table 2 - 4 List of Excipients

*Used as processing agent, does not remain in the final product.

4.4.2 Suppliers Specifications of the excipients

Microcrystalline cellulose

Specifications	
Loss on drying	% 3.0 - 5.0
Bulk density	0.26 - 0.31 g/cc
Identification	A, B Passes
Degree of polymerization, units	NMT 350
pH	5.5 - 7.0
Conductivity,	NMT 75 µS/cm
Residue on ignition,	% NMT 0.05
Water soluble substances,	mg/5g NMT 12.5
Water soluble substances,	% NMT 0.25
Ether soluble substances,	NMT 5.0 mg/10g
Heavy metals,	NMT 0.001 %
Solubility in Copper Tetrammine Hydroxide	Soluble
Microbial limits:	
Total aerobic microbial count	NMT 100 cfu/g
Total yeast and mold count, cfu/g *	NMT 20 cfu/g
Pseudomonas aeruginosa in a 10g sample	Absent

Escherichia coli in a 10g sample	Absent
Staphylococcus aureus in a 10g sample	Absent
Salmonella species in a 10g sample	Absent
Coliform species in a 10g sample	Absent
Additional FMC Specifications	
Particle size (Air Jet):	
wt. % + 60 mesh (250 microns)	NMT 1.0
wt. % + 200 mesh (75 microns)	NMT 30

Cellulose Acetate CA 398-10 NF-EP

Specifications	
ASTM A Viscosity (mPa s)	8.0 to 13.0
NF Loss on drying	% 3.0 - 5.0
NF NF Acetyl (%)	39.2 to 40.3
NF Loss on drying	5 % W Max
NF Free Acid	0.1% Max
NF Infrared Identity	Pass
NF Residue on ignition,	0.1% Max
NF Residual Solvents	Pass
EP Heavy metals,	0.001 % Max
Microbial limits:	
EP Total aerobic microbial count	10^3 cfu/g Max
EP Total yeast and mold count, cfu/g *	10^2 cfu/g Max
EP Escherichia coli in a 10g sample	Absent
EP Salmonella species in a 10g sample	Absent

Lactose Monohydrate

Specifications USP NF 23	
Identification	Pass
Appearance/color of solution	Pass
Optical rotation	+54.4 to +55.9°
Acidity or alkalinity	Pass
Heavy metals	≤5 µg/g
Absorbance 210–220 nm	≤0.25
Absorbance 270–300 nm	≤0.07
Loss on drying	≤0.5%
Water	≤1.0%
Residue on ignition	≤0.1%
Heavy metals,	NMT 0.001 %

Solubility in Copper Tetrammine Hydroxide	Soluble
Microbial limits:	
Total aerobic microbial count	NMT 100 cfu/g
Total yeast and mold count, cfu/g *	NMT 50 cfu/g
Escherichia coli in a 10g sample	Absent
Isomer ratio	Pass
Salmonella species in a 10g sample	Absent

PERLITOL Mannitol	
Specifications USP NF 23	
Melting range	164–169°C
Specific rotation	+137° to +145°
Acidity	+
Loss on drying	≤0.3%
Chloride	≤0.007%
Sulfate	≤0.01%
Arsenic	≤1 ppm
Reducing sugars	+
Assay (dried basis)	96.0–101.5%
mean diameter 180 µm	

Sodium Chloride	
Specifications USP 28	
Identification	Pass
Appearance of solution	Pass
Acidity or alkalinity	Pass
Loss on drying	0.50%
Arsenic	1 µg/g
Bromides	≤0.01%
Chloride	Pass
Barium	Pass
Nitrites	Pass
Aluminum	≤0.2 µg/ga
Magnesium and alkaline earth metals	≤0.01%
Iodide	Pass
Iron	≤2 µg/g
Sulfate	≤0.020%
Ferrocyanides	Pass
Heavy metals	≤5 ppm
Phosphate	≤0.0025%

Potassium	≤0.05%[ab]
Sterility	Pass
Assay (dried basis)	99.5–100.5%

Polyox	
Specifications USP NF 23	
Identification	Pass
Loss on drying	≤1.0%
Silicon dioxide and nonsilicon dioxide residue on ignition	≤2.0%
Silicon dioxide	≤3.0%
Heavy metals	≤0.001%
Free ethylene oxide	≤0.001%
Organic volatile impurities	Pass
Viscosity	Pass

Methocel	
Specifications USP 28	
Identification	Pass
Apparent viscosity	Pass
Loss on drying	≤5.0%
For viscosity grade >50 mPa s	≤1.5%
For viscosity grade ≤50 mPa s	≤3.0%
For type 1828 of all viscosities	≤5.0%
Heavy metals	≤0.001%
Organic volatile impurities	Pass
Methoxy content	
Type 1828	16.5–20.0%
Type 2208	19.0–24.0%
Type 2906	27.0–30.0%
Type 2910	28.0–30.0%
Hydroxypropoxy content	
Type 1828	23.0–32.0%
Type 2208	4.0–12.0%
Type 2906	4.0–7.5%
Type 2910	7.0–12.0%

Tartric Acid	
Specifications USP 23	
Identification	Pass
Specific rotation	+12.0° to +13.0°

Loss on drying	≤0.5%
Residue on ignition	≤0.1%
Organic volatile impurities	Pass
Oxalate	Pass
Sulfate	Pass
Heavy metals	≤0.001%
Assay (dried basis)	99.7–100.5%

PEG 400	
Specifications USP 23	
CAS #	25322-68-3
Description	Clear colourless liquid
Sp gravity @ 27/27 deg cel	1.110 - 1.120
Cloud Point in deg cel	Report
BP in deg cel	> 200
Flash Point in deg cel	235
pH of 1% solution	4.5 -7.0
Solubility	Soluble in water and ethanol

Polyvinyl Pyrrolidone	
Specifications USP NF	
Appearance @ 25°C	White to creamy white powder
Identification Tests	Meets all ID tests
Appearance @ 25°C (5% as is aqueous solution)	Free of haze
European Colour Test – B Colour	Pass
European Colour Test – BY6 Colour	BY6 Min
European Colour Test – R Colour	R6 Min
% Moisture (Karl Fischer)	5.0 Max
pH (5% as is aqueous solution)	3.0-5.0
% Ash (Residue on Ignition or Sulphated)	0.02 Max
ppm Vinyl Pyrrolidone (HPLC)	5.0 Max
% 2-Pyrrolidone	3.0 Max
ppm Heavy Metals (as Lead)	5 Max
ppm Aldehydes (Calculated as acetaldehyde)	500 Max
% Nitrogen (anhydrous basis)	12.0-12.8
K-Value (1% solids w/v aqueous solution)	29-32
ppm Peroxide Content (Titanyl Sulfate Method)	400 Max
ppm Hydrazine	1.0 Max
Salmonella species in a 10g sample	Absent
Coliform species in a 10g sample	Absent
Micorbial Limit Test Specifications	
Total Aerobic Plate Count, CFU/g	100 Max

Mould/Yeast, CFU/g	100 Max
Salmonella, CFU/g	Negative
Staphylococcus Aureus CFU/g	Negative
Pseudomonas aeruginosa, CFU/g	Negative
E.Coli, CFU/g	Negative

Purified Talc	
Specifications USP NF	
Identification	Complies with EP/BP tests
Acidity or alkalinity	
Change colour to pink	NMT 0.3 ml of 0.01 M NaOH
Water-soluble substances	Max 0.2%
Aluminium	Max 2.0%
Calcium	Max 0.90%
Iron	Max 0.25%
Lead	Max 10.0 ppm
Magnesium	17.0% to 19.5%
Loss on ignition	Max 7.0%
Microbial contamination	
Total viable aerobic count	NMT total of 10^2 bacteria and fungi per gram.

Aerosil 200	
Specifications USP NF 23	
Identification	Pass
pH (4% w/v dispersion)	3.5–5.5
Arsenic	8 µg/g
Loss on drying	2.50%
Loss on ignition	2.00%
Organic volatile impurities	Pass
Assay (on ignited sample)	99.0–100.5%
Specific Surface Area	200 ± 25 m^2/g
Tapped Density	0.05 g/cm^3

Sorbitol	
Specifications USP NF 23	
Identification	Pass
pH	3.5 – 7.0
Appearance of solution	Pass
Chloride	0.005%
Sulfate	0.01%
Bacterial	$10^3/g$

Fung	$E10^2/g$
Bacterial endotoxins	Pass
Nickel	1 µg/g
Organic volatile impurities	Pass
Reducing sugars	0.30%
Residue on ignition	0.10%
Water	1.50%
Assay (anhydrous basis)	91.0–100.5%

Magnesium Stearate	
Specifications USP NF 23	
Identification	Pass
Microbial limits	
Aerobic microbeal Count	$10^3/g$
Fungi and yeasts	500/g
Acidity or alkalinity	Pass
Specific surface area	Pass
Loss on drying	6.00%
Chloride	0.10%
Sulfate	1.00%
Lead	0.001%
Relative stearic/palmitic content	Pass
Organic volatile impurities	Pass
Assay (dried, as Mg)	4.0–5.0%

Ingredients	Approval Status (USFDA)	Qty (mg)
Sorbitol	Oral; tablet	337.28
Cellulose acetate CA-398-10	Oral; tablet, extended release (pending)	47.49
Polyethylene glycol 400	Oral; tablet	105.065
Cellulose, microcrystalline	Oral; table	1385.3
Lactose monohydrate	Oral; tablet, film coated	587.44
Sodium chloride	Oral; tablet, extended release	335.1
Talc	Oral; tablet, extended release	80
Silicon dioxide, colloidal	Oral; tablet	99
Mannitol	Oral; tablet	991.77
Magnesium Stearate	Oral; tablet	150 mg
Sodium Chloride	Oral; tablet	148 mg

Table 3 - 4 Approval status of the inactive ingredients used for Oral Route

4.4.3 Drug excipients compatibility study:

At an early stage of proposed drug product development, drug-excipient compatibility study performed, to identify the potential incompatibilities of drug with the excipients intended to be used for product development. The pre-formulation study was based on the excipients to be used in the finished product. All the inactive ingredient guide (USFDA) approved ingredients were selected for the study as mentioned in table 3-4.

Butorphanol tartrate was mixed with Lactose and mannitol in Drug to Excipient ratio of 1:5 W/W and Other excipients in Drug to Excipient ratio of 5:1 proportion. Binary mixture and the blend were exposed to 40°C /75%RH temperatures for 4 weeks to accelerate drug degradation and interaction with excipients in USP type I amber glass vials with LDPE (low density polyethylene) stopper for evaluation of their compatibility at stress condition. The blends exposed to stress conditions were compared with their respective initial blend stored at controlled condition by physical observation. The samples are then characterized for the drug content, which were determined quantitatively using developed analytical method after dissolving the drug in water and percentage drug content verified initially and after 4 weeks and compared.

Results of drug-excipient compatibility study are described below in table

Drug : Excipients	Initial		4 Week 40°C /75%RH	
	Observation	% Drug Content	Observation	% Drug Content
Butorphanol Tartrate	White to off-white Crystalline powder.	100.35	White to off- white, free flowing powder. No change in physical appearance observed	99.49
Butorphanol Tartrate & CA 398-10	White to off-white Crystalline powder.	100.28	White to off- white, free flowing powder. No change in physical appearance observed	101.34
Butorphanol Tartrate & Magnesium Stearate	White to off-white, free flowing powder.	101.34	White to off- white, free flowing powder. No change in physical appearance observed	100.85
Butorphanol	White free	100.32	White to off- white, free	99.62

Drug :	Initial		4 Week 40°C /75%RH	
Tartrate & Kollidon K 30	flowing powder.		flowing powder. No change in physical appearance observed	
Butorphanol Tartrate & Sodium Chloride	White to off-white, free flowing powder.	100.74	White to off- white, free flowing powder. No change in physical appearance observed	100.64
Butorphanol Tartrate & Lactose	White to off-white, free flowing powder.	102.75	White to off- white, free flowing powder. No change in physical appearance observed	101.73
Butorphanol Tartrate & Purified Talc	White to off-white, free flowing powder.	99.25	White to off- white, free flowing powder. No change in physical appearance observed	97.35
Butorphanol Tartrate & D-Sorbitol	White to off-white, free flowing powder.	100.34	White to off- white, free flowing powder. No change in physical appearance observed	101.24
Butorphanol Tartrate & Colloidal Silica	White to off-white, free flowing powder.	100.48	White to off- white, free flowing powder. No change in physical appearance observed	102.42
Butorphanol Tartrate & Mannitol	White to off-white, free flowing powder.	97.51	White to off- white, free flowing powder. No change in physical appearance observed	95.20
Butorphanol Tartrate & PEG 400	White to off white colour lump.	100.31	White to off white colour lump. No change in physical appearance observed	101.52
Butorphanol	White to off-	101.60	White to off- white, free	100.30

Drug :	Initial		4 Week 40°C /75%RH	
Tartrate & MCC 101	white, free flowing powder.		flowing powder. No change in physical appearance observed	
Butorphanol Tartrate & Acetone	White to off white colour lump.	99.66	White to off white colour lump. No change in physical appearance observed	97.63
Butorphanol Tartrate & Isopropyl alcohol	White to off white colour lump.	101.88	White to off white colour lump. No change in physical appearance observed	100.61
Butorphanol Tartrate & Purified water	White to off white colour lump.	101.36	White to off white colour lump. No change in physical appearance observed	103.52

Table 4 - 4 Drug excipient compatibility Results

Conclusion : Under mentioned accelerated conditions (40°C /75%RH for 4 weeks), butorphanol tartrate did not reveal show sharp fall in content so it can be concluded that it do not show any incompatibilities with the proposed excipients as summarized in table 4 -4. Preformulation studies show that the selected excipients are compatible with Butorphanol tartrate

Differential scanning Calorimetry

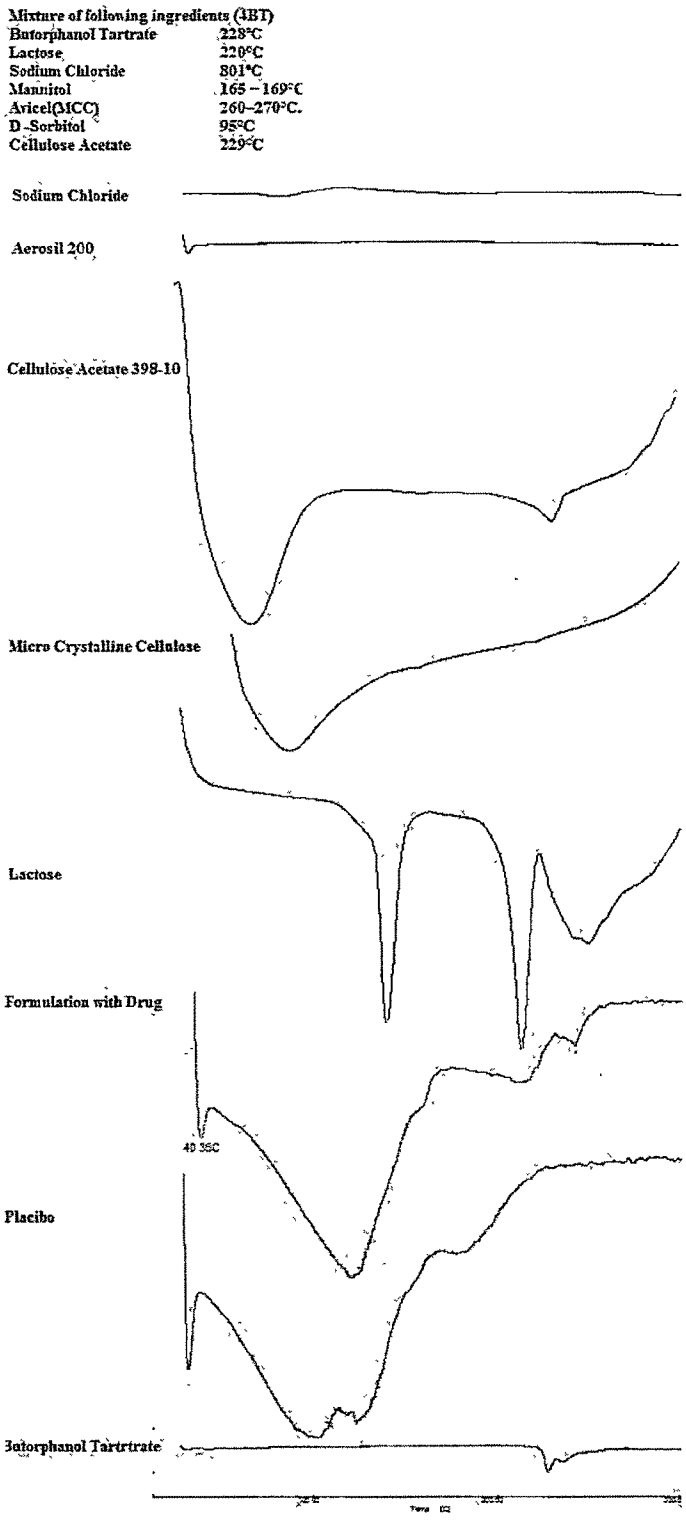


Figure 1 - 4 DSC Study

The DSC of samples was carried out by scanning the samples using differential scanning colorimeter (Mettler). Thermograms were analyzed using Mettler Toledo star SW 7.01. An empty aluminium pan was used as the reference for all measurements. During each scan, 2 to 3 mg of sample was heated, in a hermetically sealed aluminium pan. DSC studies were performed under nitrogen flush at heating rate of 10 °C from 35 °C to 300 °C to investigate the any incompatibility between drug and excipients.

DSC curve of lornoxicam exhibited sharp endothermic peak at 228° C, which is due to melting of Butorphanol Tartrate.

For that DSC of plain drug was done followed by DSC study of individual excipients to be used in dry form. i.e. aerosil 200, Cellulose acetate 398-10, Sodium Chloride, Lactose, MCC and drug mixed with placebo formulation was done.

Conclusion:

Formulation composition DSC shows exhibited a sharp melting endotherm & plain drug melting endotherm can be observed in figure 1 – 4 that shows no changes observed in the formulation & the original plain drug melting endotherm which exhibited a sharp melting endotherm at (228°C). Hence it was clear that there is no specific interaction between the drug and excipients used in the formulation. Melting endotherm of Cellulose acetate and drug are nearer but it is not showing any signs interaction, no change in intensity of peak observed. Minor shift in melting point can be observed which is not indicative of interaction. Melting peak of PVP k 30, magnesium Stearate, Mannitol, Sorbitol, Micro Crystalline Cellulose observed at 150, 89, 167,95, 280 °C respectively in the placebo.

4.5 Drug Product Formulation Development:

The proposed target for formulation development must be easy to manufacture, chemically and physically stable throughout the manufacturing process, product shelf life and bio-available in predicted manner. During design of the formulation, critical formulation and manufacturing variables were identified and adjusted to yield quality product. Design of experiments was used to improve and establish the robustness of the formulation around target formulation.

Butorphanol tartrate osmotic Pump 10 mg, the proposed drug product is intended to have following primary attributes:

- Product may to be formulated as coated tablet dosage form or matrix tablet.
- Product is developed as an coated dosage form where coating shall semi permeable in nature and must comply with the following release specifications:

4.5.1 Predicted Plasma concentration of Butorphanol Tartrate

From data of oral IR plasma concentration of drug available in literature total amount of drug required to achieve steady state level in particular time frame is found out. The target release profile was decided from the AUC of the oral immediate release blood concentration data by Wagner nelson de-convolution process and is shown in figure 2-4. The target drug release profile is depicted in table 5 -4 & 6 – 4.

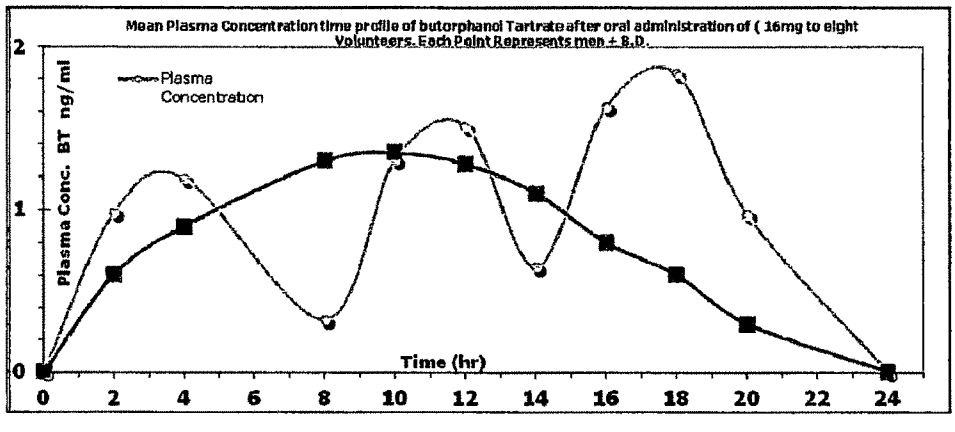


Figure 2 - 4 Predicted Plasma concentration of Butorphanol Tartrate

Above mentioned graph shows actual plasma concentration time profile after administration of three IR formulation administration at the interval of 7 hours and from the plasma concentration of the IR formulation plasma concentration time profile of ER formulation predicted considering pharmacokinetic data. From the data of ER plasma drug concentration profile In-vitro target release profile was calculated through deconvolution.

Time Hr	Target *In-vitro* Drug release
0	0.00
2	3.00
4	15.00
8	28.00
10	57.00
12	70.00
14	82.00
16	90.00
18	95.00
20	99.00
22	99.00

24	100.00

Table 5 - 4 Target release profile (Detail)

Time (hr)	Target Range Cum. % release profile
2	NMT 15
4	10 to 30
8	30 to 55
14	50 to 80
21	NLT 90

Table 6 - 4 Target release profile (Brief)

Drug Name : Butorphanol Tartrate			**Dosage Form :** Extended Release		
Stage	**USP Apparatus**	**Speed**	**Medium**	**Volume (ml)**	**Recommended Sampling Times**
Stomach	II (Paddle)	50	0.1 N HCl Followed by	250 ml	120 minutes Followed by
Intestine	II (Paddle)	50	6.8 pH Phosphate Buffer	250 ml	up to 24 Hrs in buffer stage

Table 7 - 4 Dissolution conditions

4.5.2 Quality Target Product Profile (QTTP) :

As a target for the development of a manufacturing process, the following attributes were identified that will ensure the desired product quality to match all aspects of Quality target product profile:

1. Correct amount (assay) of drug substance in the drug product.
2. Content Uniformity
3. Weight variation of the drug product.
4. Dissolution (Conditions mentioned in table 7 – 4) of drug substance from the drug

product. (Target release profile table 5 -4 & 6 – 4).

5. Type and concentration of excipients that directly influences the quality and performance of the drug product.

6. Container closure system to provide intended protection to drug product.

7. Overages if required

8. Hardness : 2 – 5 kg/cm^2

9. Friability NMT 1.0 %

10. Bulk density and tapped density (Granules)

4.5.3 Selection of Manufacturing Process:

Trials were initiated with dry granulation method but sufficient hardness could not be achieved dry granulation method so further trails were done with wet granulation method.

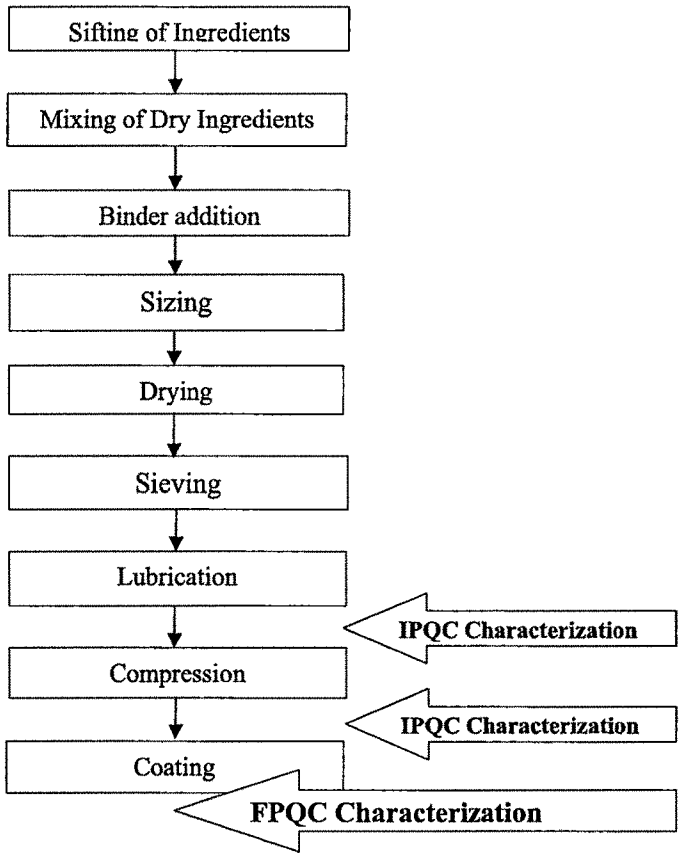
The wet granulation method was selected for the manufacturing of core tablets.

Drug substance sourced as USP grade and evaluated for physio-chemical and analytical parameters as per IH method of analysis.

Preparation method of core tablets

Core tablets were prepared by wet granulation and the composition is given in table 1. For preparation of core tablets, the batch size was kept as 1000 tablets. The mixture was moistened with PVP solution in isopropyl alcohol and granulated by passing through 18 sieve. The granules were dried at 50°C (approximately 1 h) after which they were passed through 25 sieve. These sized granules were then blended with magnesium stearate, talc and aerosol 200 (all 100 sieve passed) and compressed into tablets using a rotary tablet compression machine (General Machinary Company, India) fitted with 9 mm std concave punches.

4.5.4 Process Flow Chart



4.5.5 Unit Operations of the Preparation process

Granulation

Sieving : All the excipients were sieved before use to break the agglomerates sieve sizes used for sieving are mentioned in table 8 - 4.

Following sieve was used for the same.

Excipients	Sieve Size
Butorphanol Tartarate	40 #
Mannitol	60 #
Lactose	40 #
NaCl	40 #
MCC 101	40 #
PVP K 30	40 #
Mg. Stearate	100 #

Talc	100 #
Aerosil 200	100 #

Table 8 - 4 Sieving Details

Dry Mixing : Drug was mixed with other excipients using geometric dilution method followed by sieving through 40 # twice to have uniform mixing.

Binding : For binding Polyviny Pyrrolide was dissolved in IPA 10% w/v and 120 ml of this solution was used for binding. Binding was performed till wet mass with granular consistency obtained.

Sizing : Sizing was done in 18# sieve. (Wet Milling)

Drying : Drying was done at 50°till LOD is achieved NMT 3%.

Sieving : Dry granules were again passed through 25.

Lubrication : Talk,aerosil and Magnesium stearate were added in sequence respectively and blended for 5 min in poly bag to get uniform coating on the granules.

Characterization : Assay, Blend uniformity, LOD, Bulk Density, Tapped Density.

Compression : Compression was done on 8 Station rotary tablet compression machine from general machinery company.

Compression Parameters : 9 mm standard concave punch plain on both sides

Turret Speed : 9 RPM

Compaction Force: 4 – 5 kg

Thickness Adjustment Lever: Optimised to 3.1 to 3.3 mm thickness.

4.5.6 Optimisation of osmogen composition in the core

	Core Formula mg/Tab						
	A	B	C	D	E	F	G
Butorphanol Tartrate	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Mannitol			100.00	100.00		100.00	

Lactose		100.00		100.00	100.00		
NaCl	100.00				100.00	100.00	
MCC 101	100.00	100.00	100.00				200.00
PVP K 30	12.00	12.00	12.00	12.00	12.00	12.00	12.00
Mg. Stearate	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Purified Talc	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Aerosil 200	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Total	**230.00**	**230.00**	**230.00**	**230.00**	**230.00**	**230.00**	**230.00**

Table 9 - 4 Composition of core for optimisation of osmogen

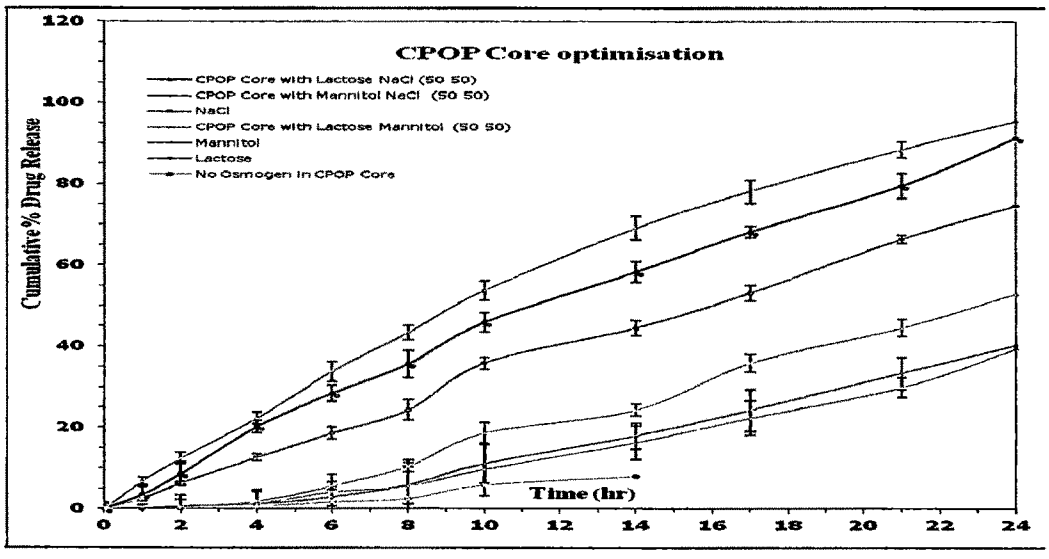


Figure 3 - 4 Drug release from CPOP with different osmogen in core

Effect of osmogen and combination thereof on drug release:

During initial development it was necessary to fix the osmogen within the core and core composition with its manufacturing procedure. Osmotic pressure of some osmogen and combination thereof were evaluated for degree of osmosis keeping manufacturing process and composition (Table 9-4) except osmogen trials were taken and subjected to dissolution as mentioned in table 7 -4, the graph Figure 3 -4 plotted to optimised the prototype batch.

Sr. No.	Compound/ mixture	Osmotic pressure (Atm)
1	Sodium Chloride: Mannitol (1:1)	365++

2	Sodium chloride :Lactose (1:1)	365+
3	Sodium chloride	356
4	Mannitol:Lactose (1:1)	130
5	Mannitol	38
6	Lactose	23

Table 10 - 4 Osmotic pressure exerted by saturated solution of compounds

Table 10 – 4 shows Osmotic pressure exerted by saturated solution of compounds used for developmental studies. Lactose, mannitol and sodium chloride separately and in combination with each other in equal ratio were used as osmogen in the core tablet and its effect on drug release was determined keeping other parameters constant i.e thickness of coating (weight gain) and pore forming agent level constant. Theoretically osmotic pressure exerted by the osmogen is in following order. NaCl & Lactose (1: 1 Combination) > NaCl & Mannitol (1: 1 Combination) > NaCl > Lactose & Mannitol (1: 1 Combination) > Lactose > Mannitol. It is apparent from Figure 3 -4 that as osmotic pressure of osmogen enhances the drug release when used in constant amount and thus had a direct effect which might be due to the increased water uptake and hence increased driving force for drug release. Combination of Lactose and NaCl in equal proportion was showing fastest drug release and was considered further for optimization.

4.5.7 Optimisation of coating

Coating process

Coating process varies with type of coating system, manual pan coating with gun spray is Require skills and may induce variability specifically for functional coating. Therefore, Perforated pan make Solace Autocoater was used for coating for better reproducibility in functional coating. It requires coating load of at-least 1 kg. To increase the coating load dummy tablets with smaller size were used with active tablets. Increasing coating load leads to decreased coating variation and increased uniformity of coating. Due to previous experience and coating process optimised on dummy tablet

Coating Ingredients

Following substance were opted for preparation of Coating Solution

Cellulose acetate is widely used in pharmaceutical formulations both in sustained-release applications and for taste masking. Cellulose acetate is used as a semipermeable coating on tablets, especially on osmotic pump type tablets and implants. This allows for controlled, extended release of actives from the osmotic pump. Cellulose acetate films, in conjunction with other materials, also offer sustained release without the necessity of drilling a hole in the coating as is typical with osmotic pump systems.

Cellulose acetate occurs as a white to off-white powder, free-flowing pellets, or flakes. It is tasteless and odourless in nature. The solubility of cellulose acetate is greatly influenced by the level of acetyl groups present. In general, cellulose acetates are soluble in acetone–water blends of varying ratios, dichloromethane–ethanol blends, dimethyl formamide, and dioxane. The cellulose acetates of higher acetyl level are generally more limited in solvent choice than are the lower-acetyl materials. Cellulose acetate is compatible with the following plasticizers: diethyl phthalate, polyethylene glycol, triacetin, and triethyl citrate.

In this formulation Cellulose acetate 398-10 was used with acetyl content of 39.8%.

Sorbitol occurs as an odorless, white or almost colorless, crystalline, hygroscopic powder with density 0.448 g/cm^3. It is used as a diluent in tablet formulations. Sorbitol is a very hygroscopic powder and relative humidities greater than 60% at 25°C. Sorbitol also has been used as a plasticizer in film formulations. Sorbitol is soluble in water and insoluble in ether and slightly soluble in ethanol.

Plasticizers are used in polymeric coating dispersions to optimize properties of the film such as permeability, hydrophobicity, adhesiveness, flexibility and brittleness. Three commonly used plasticizer types are polyethylene glycols (PEGs), fixed oils (e.g.: Castor oil, Oleic acid) and organic esters (e.g.: Triacetin, Tributyl citrate). Plasticizers are known to affect the Tg of the polymer. Some plasticizers such as glycerin or PEG 400 are water soluble while others are not. PEG 400 (Plastisizer) Polyethylene glycols are stable, hydrophilic substances The presence of polyethylene glycols in film coats, especially of liquid grades, tends to increase their water permeability. Polyethylene glycols are useful as plasticizers pharmaceutical products to avoid rupture of the coating film.

Dibutyl Sebacate which is is a clear, colorless, oily liquid used in oral pharmaceutical formulations as a plasticizer soluble in ethanol (95%), isopropanol, and mineral oil; practically insoluble in water.

Solvent Selection

Combination of Acetone and water in different proportions were tried to have coating solution with cellulose Acetate CA 398-10, D-Sorbitol and Dibutyl Secabate. So, acetone and water were selected as final solvents.

Solid content

This parameter has immense impact on uniformity of coating. 4% solid content was confirmed through literature and trial of coating was conducted on dummy tablet to confirm the same.

4.5.7.1 Optimisation of level of pore former in the coating membranes.

To study the effect of increasing level of pore former sorbitol, core tablets were coated with varying coating composition 17, 27, 37 and 47% (w/w) of D - sorbitol. For this study lactose and NaCl in equal proportion were taken as optimised before. And coating thickness (% weight gain) was kept constant at 5 %.

Coating Components		Formulation Code			
		Ratio of Polymer, pore former and plasticizer in solid			
		BT1	BT2	BT3	BT4
Total Solids (4 %W/W)	CA	40 %	50 %	60 %	70 %
	D –Sorbitol	47 %	37 %	27 %	17 %
	PEG 400	13 %	13 %	13 %	13 %
Acetone		86 % w/w			
Water		10 % w/w			
Solid		4 % w/w			

Table 11 - 4 Composition of coating for optimisation of coating solution composition

Sorbitol being soluble in nature, on contact with dissolution medium dissolves immediately and forms channels in the coating through which drug can come out though simple diffusion. It was found that pore-former ratio has direct impact on drug release and level of pore former increases simultaneously (Figure 4-4). The drug release increases with the increase in the concentration of the pore former. At levels up to 27% and 37% (w/w) of pore former, numbers of pores were not sufficient to contribute to significant drug release. On the other hand, membrane that contained 47% (w/w) of pore former; the release profile was faster since it became highly porous after coming in contact with aqueous media. On further increasing the pore-forming agent the coating membrane lost its release retardant properties. Considering that 37% of pore former (D – sorbitol) was considered for further optimisation of formulation.

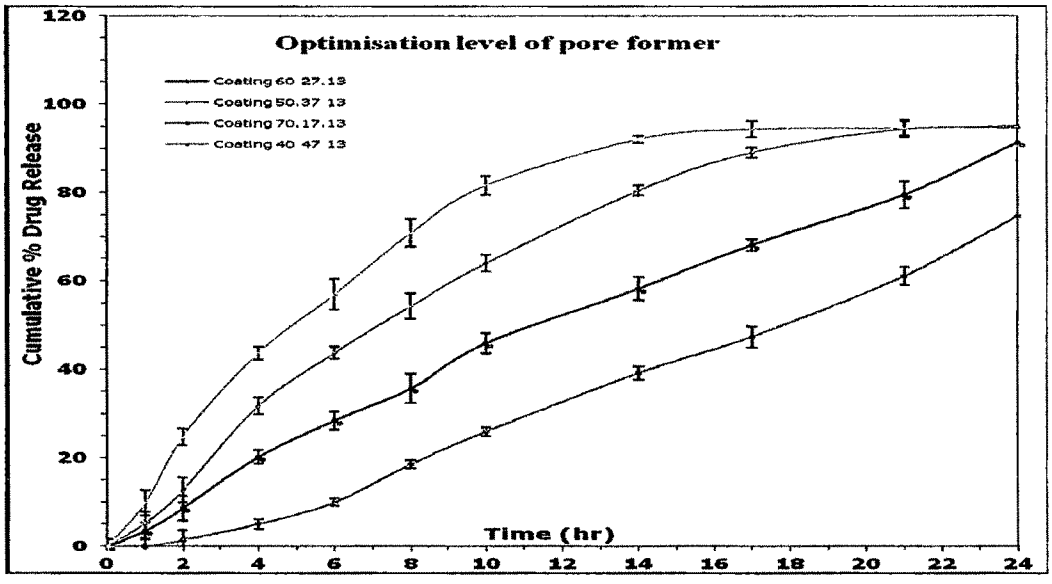


Figure 4 - 4 Drug release from various coating compositions

4.5.7.2 Optimisation of coating thickness (Weight gain)

In many cases coating has barrier properties and coating in-process is verified by weight gained by the system in stipulated time period. Because of barrier properties coating thickness will have direct impact on drug release. To study the effect of weight gain during coating on drug release, core tablets containing equal proportions of Lactose and Sodium chloride and were coated with coating solution containing 37 % w/w of pore forming agent to achieve a weight gain of 3, 6, 9, 12, 15 % w/w of the total solid contents of coating. The *in vitro* release was shown in figure 5-4. It was observed that drug release decreases with an increase in weight gain (Coating Thickness) of the membrane. 3 and 6 % of coating shows higher variations (Higher SD) where as 9, 12 and 15 % don't show such variations.

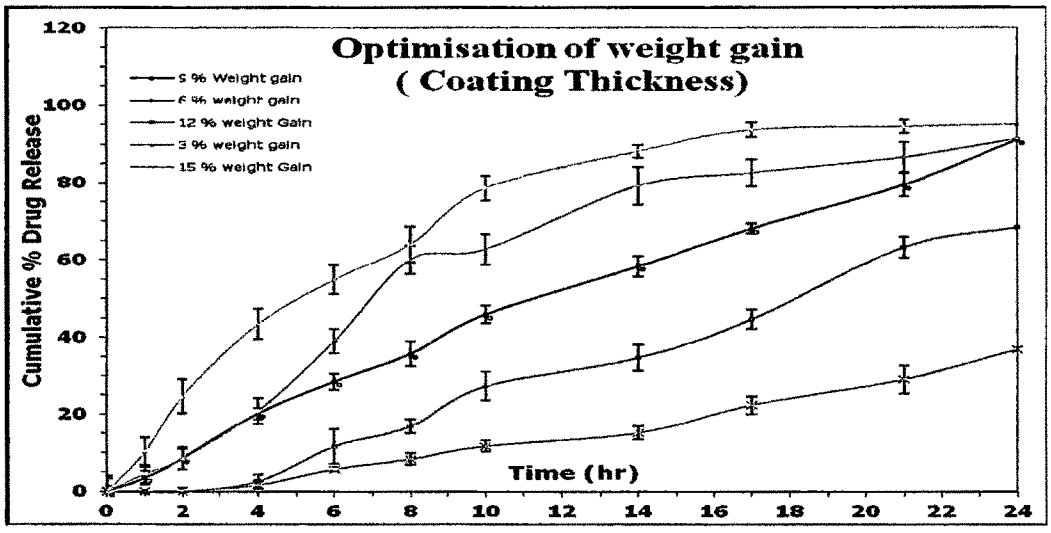


Figure 5 - 4 Drug release from variable coating thickness

Thickness of cross section of exhaused shell after dissolution was measured in SEM analysis which shows that optimised formulation has coating thickness of 100 ± 10 µm.

4.5.7.3 Optimised Coating Formula & Preparation method

Table 12 – 4 shows optimised coating composition based on previous experimentation.

Coating Formula	
Cellulose Acetate	50 % w/w
D -Sorbitol	37 % w/w
PEG - 400	13 % w/w
Ratio of Acetone : Water : Solid	
Acetone	86.00 % w/w
Water	10.00 % w/w
Solid	4.00 % w/w

Table 12 - 4 Optimised coating composition

Coating solution preparations:

Step 1: Cellulose acetate CA 398-10 was dissolved in Acetone.

Step 2: PEG 400 dissolved in 25% quantity of water.

Step 3: D-solrbitol dissolved in 25% quantity of water.

Step 4: PEG 400 solution was added in D-Sorbitol Solution slowly. Make clear solution by addition of more 25% of water.

Step 3: Very slowly add solution received in Step-4 to solution received in Step 1 drop by drop. Add remaining quantity of water. Do not add further water if precipitates remains for fore then 5 Sec.

Parameter	Value
Solvent	Acetone : Water (86 : 10)
Solids content (%w/w)	4 %
Weight gain (%)	6 %

Table 13 - 4 Optimised Coating solution parameters

Coating Machine Parameters

Parameter	Value	Justification
Fluid nozzle (mm)	1.5	Fixed Machine Parameter
Spray pan size (Inch)	12 "	Fixed Machine Parameter
Baffles (Nos.)	6	Fixed Machine Parameter
Inlet air CFM	28-32	Shall be lower than Outlet
Outlet air CFM	42-46	Shall be higher than Inlet to carry solvent outside.
Inlet air temperature (°C)	50 - 55 °C	Selected considering solvent to be evaporated
Out let air temperature (°C)	45-50 °C	Output
Pre-warm tablet bed (°C)	40-43 °C	Curing
Tablet surface bed temp (°C)	39-42 °C	Curing effect Result
Atomizing air pressure (kg/cm^2)	3 -4 kg/cm^2	Studied on dummy considering Broadness of the spray from the spray gun

Table 14 - 4 Coating machine parameters

Gun-to-bed distance (Inches): Furthest possible Gun-to-bed distance was used on reducing this distance the spray pattern was observed getting narrow.

Spray Rate / Paristaltic Pump RPM: Least achievable paristaltic pump speed was 6 RPM at which the spray was pulsative and Very high speed i.e. 16 RPM was resulting in very high spray rate. On 10 to 12 RPM paristaltic pump speed was optimum to have uniform coating.

Perforated Coating pan Speed: Through coating trials on dummy tablet Perforated Coating pan speed was optimised to 3.8 to 4.2 RPM.

Coating Parameters	
Gun-to-bed distance (inches)	3.5 ± 0.5
Spray rate (g/min)	4.0 ± 0.5 g\min
Pan speed (rpm)	4.0 ± 0.2 RPM
Peristaltic Pump RPM	11 ± 1 RPM

Table 15 - 4 Coating Variables

Tablet Surface bed Temperature:

An acceptable product temperature range was identified. In the studied range, drug-layered beads with consistent quality were produced. Spray drying and agglomeration were minimized. Product temperature is a scale-independent parameter and can be applied to other scales. The risk of product temperature to impact the assay of the drug-layered beads is low.

Air volume

Air volume range was identified and an optimal fluidization pattern was achieved. In the studied range, drug-layered beads with consistent quality were produced. Air volume is a scale-dependent parameter.

Spray rate

Spray rate is critical process parameter. Spray rate range 3.5 to 4.5 g/min was studied for it's impact on drug release, coating with consistent quality was produced at the 600gm scale. Spray rate is a scale dependent parameter. The spray rate per nozzle shall be kept the same if processing equipment change from an 12" perforated coating pan. The total spray rate can be increased to any fold by multiplying spray guns.

Atomization air pressure

Atomization air pressure was identified as critical process parameter affecting coating quality and so drug release critical quality attribute. The range of Atomization air pressure studied for consistent coating quality at the 600 gm scale. Attrition was minimized. Atomization air pressure

is an equipment-dependent parameter. As this is a scale-out process and each of the three nozzles used in the 12" solace coater shall be kept constant.

Table 13-4, 14-4 and 15-4 shows coating parameters and machine parameters as discussed are critical process parameters for coating to achieve quality target product profile (QTTP).

4.6 Results:

The results of characterization at pre-compression (granules) stage for Assay, Bulk Uniformity (BU), Water content(WC), Loss On Drying (LOD), Bulk Density (BD) & Tap Density(TD) are summarized in table 16-4.

The results of characterization after compression (Core Tablet) for Description, Average Weight (mg), Assay (%), Water Content, Hardness (kg/cm2), Friability (%), Thickness (mm), Diameter (mm), Uniformity of content are mentioned in table 17-4.

The results of characterization after coating (coated Tablet)all above parameters and dissolution are mentioned in table 18-4.

4.6.1 Pre-compression characterization:

Parameter	Limits	Result
Assay	95.00 to 105.00 %	101.23
Bulk Uniformity	Minimum 90 %	Minimum 97 %
	Maximum 110 %	Maximum 107 %
	Mean 95 % to 105 %	Mean 102.97 %
	RSD 5 %	RSD 2.71 %
Water Content	NMT 5%	3.0
LOD	NMT 3%	1.6 %
Bulk Density	0.40 - 0.50 gm/ml	0.44 gm/ml
Tapped Density	0.55 - 0.65 gm/ml	0.61 gm/ml

Table 16 - 4 Results of analysis at precompression stage

4.6.2 Characterization of Core Tablets

Parameters	Limit	Result
Observed in stability		
Description	White colored, circular, biconvex, uncoated tablet. plain on both side	Complies
Average Weight (mg)	Target – 230 mg 230 ± 3%	233.60 mg
Assay (%)	95 to 105	100.26
Water Content	NMT 5%	2.9
Not observed in stability		
Hardness (kg/cm^2)	4 - 6	5
Friability (%)	NMT 0.10	00.01
Thickness (mm)	3.10 – 3.30	3.18 mm
Diameter (mm)	9.0	9.00 mm
Uniformity of content	Minimum : 90.00 %	Minimum : 100.24
	Maximum : 110.00 %	Maximum : 102.03
	Average : 95 to 105 %	Average : 101.55
	% RSD NMT 5%	% RSD : 3.02

Table 17 - 4 Results of analysis of croe tablet

4.6.3 Characterization of Coated CPOP:

Parameters	Limit	Result
Observed in stability		
Description	White colored, circular, biconvex, coated tablet. plain on both side	Complies
Average Weight (mg)	Target – 245 mg 245 ± 3%	242.60 mg
Assay (%)	95 to 105	101.62
Water Content	NMT 5%	2.9 %

% Drug Dissolved	2 Hr	NMT 15%	9.1 %
	4 hr	10-30%	20.3%
	8 hr	30 to 55 %	36.2 %
	14 hr	50 to 80 %	58.8%
	24 hr	NLT 80	91.3 %
Not observed in stability			
Hardness (kg/cm^2)		5-8	7
Friability (%)		NMT 0.10	00.00
Thickness (mm)		3.40 – 3.60	3.52 mm
Diameter (mm)		9.2	9.20 mm
Uniformity of content		Minimum : 90.00 %	Minimum : 99.72
		Maximum : 110.00 %	Maximum : 101.98
		Average : 95 to 105 %	Average : 100.97
		% RSD NMT 5%	2.86

Table 18 - 4 Finished product analysis results

Developed formulation meets the predefined quality target product profile at can be formulated repetitively through effective control of critical process parameters however; large scale production may require some changes in the process depending on scale.

4.6.3.1 Thickness of exhausted Coating membrane through SEM analysis:

Exhausted shell after dissolution was broken and cross section of that was observed under SEM. Thickness of cross section of exhausted shell after dissolution was measured in SEM analysis (figure 6-4)which shows that optimised formulation has coating thickness of 100 $\pm$ 10 µm.

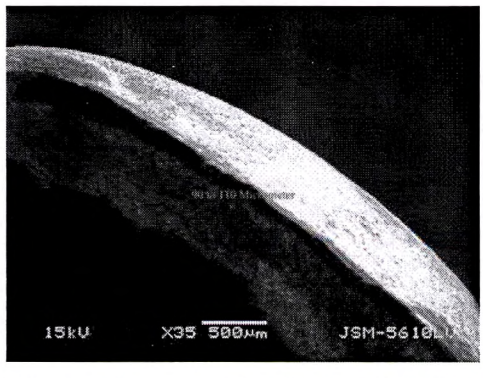


Figure 6 - 4 SEM Image of cross sectionof exhausted shell after dissolution

4.6.3.2 Effect of pH on drug release

Optimised formulation was subjected to drug release at different pH i.e. PBS 6.8 (SIF), 0.1 N HCL (SGF), acetate buffer pH 4.5, water and combination of SGC for 2 hr followed by SIF. The resulted were plotted against time the figure 7-4 shows graph plotted and table 19-4 shows summarized results.

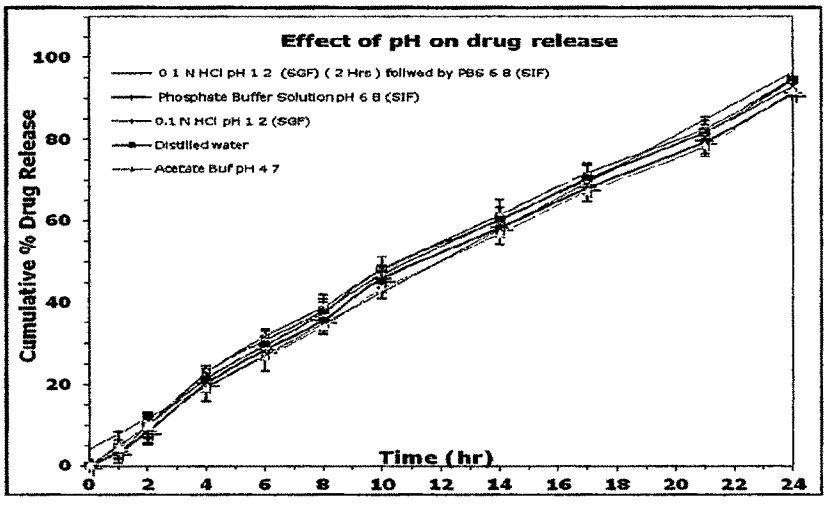


Figure 7 - 4 Drug release - effect of pH

Effect of pH on drug release										
Time (hr)	PBS pH 6.8 (SIF)	SD	0.1 N HCl pH 1.2 (SGF)	SD	Acetate Buf pH 4.7	SD	SGF 2 Hrs + SIF	SD	DW	SD
1	3.51	1.46	5.04	1.38	4.57	1.19	3.33	1.33	3.47	1.46
2	8.57	1 77	10.21	1.47	10 01	3.79	8.83	1.30	9.96	1.89
4	20.23	2.89	22.84	3.07	19.09	2.07	22.84	3.63	21.42	2.89
6	28.48	1.47	31.73	1.79	26.78	3.06	30.79	1.85	29.49	2.42
8	35.69	2.06	38.90	1.89	34.18	3.60	37.89	2.33	37.54	2.34
10	45.91	3.29	48.04	1.96	43.29	2.00	46.89	2.34	48.23	4.40
14	58.30	2.28	61.35	3.17	56.81	2.24	60.26	2.00	60.17	2.99
17	68.11	2.57	71.69	3.97	67.21	2.57	70.03	1.47	70.46	3.16
21	79.50	1.34	82.55	2.09	78.33	2.58	81.80	1.10	81.82	3.65
24	91.24	3.09	94.76	2.83	91.87	2.58	92.85	2.72	94.51	1.66

Table 19 - 4 Drug release data effect of pH

Discussion

Osmotic drug delivery is considered to be a delivery system which gives constant drug release irrespective of pH of the release media. The drug release from optimised formulation was confirmed in various release media i.e. PBS pH 6.8 (SIF), 0.1 N HCl pH 1.2 (SGF), Acetate Buf pH 4.7, SGF 2 Hrs + SIF and distilled water.

It is clearly evident from (table) that the release of BT from CPOP is independent of the pH of the medium.

The $f1$ and $f2$ values were found to be $f1$ 5.09 and $f2$ 76.02 (between PBS pH 6.8 (SIF) and 0.1 N HCl pH 1.2), $f1$ 8.09 and $f2$ 69.86 (between 0.1 N HCl pH 1.2 (SGF) and Acetate Buf pH 4.7), $f1$ 6.19 and $f2$ 74.72 (between Acetate Buf pH 4.7 and SGF 2 Hr followed by SIF), $f1$ 1.72 and $f2$ 92.55 (between SGF 2 Hr followed by SIF and distilled water) and $f1$ 4.01and $f2$ 82.91 (between distilled water and PBS pH 6.8)

Hence, it can be expected that the release from the developed formulation will be independent of the pH of the absorption site.

4.6.3.3 Effect of Agitation intensity

Optimised formulation was subjected to drug release at different rotational speed of 50, 100 and 150 RPM under PBS 6.8 (SIF) combination of SGC for 2 hr followed by SIF. The resulted were plotted against time the figure 8-4 shows graph plotted and table 20-4 shows summarized results.

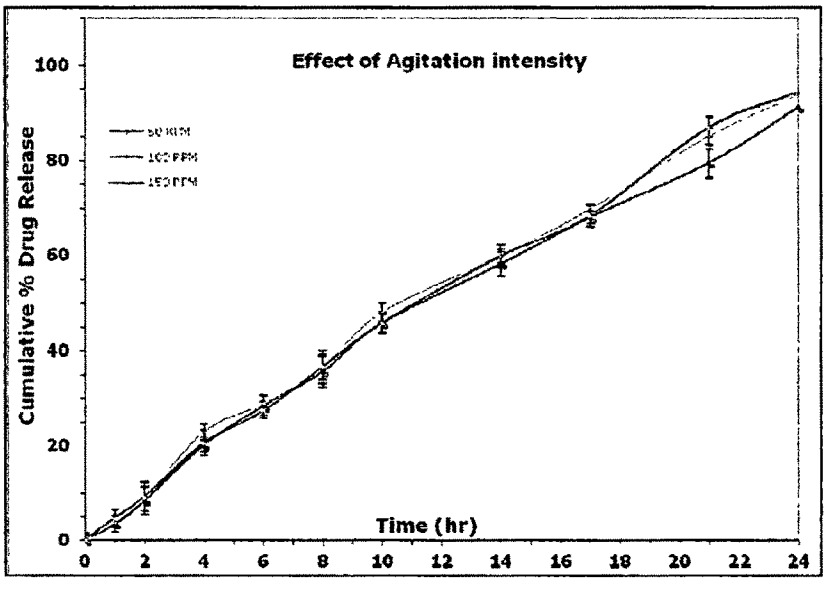


Figure 8 - 4 Drug release - effect of agitation intensity

Effect of Agitation intensity						
Time (hr)	50 RPM	SD	100 RPM	SD	150 RPM	SD
1	3.51	1.46	3.96	0.87	4 89	1.01
2	8.57	1.77	9.07	1.28	9.35	1 71
4	20.23	2 89	22.91	3 37	20 60	2.95
6	28 48	1.47	28.95	1 67	27.48	2.64
8	35 69	2.06	36 60	1.71	36.60	1.71
10	45.91	3 29	48.06	2 65	45.91	3.29
14	58.30	2 28	59.95	1.99	59.95	1.99
17	68 11	2.57	69 73	1.38	68 44	2.38
21	79.50	1.34	85.08	1.31	87.08	2.16
24	91.24	3.09	93.81	1.77	94.48	2.19

Table 20 - 4 Drug release data - effect of agitation intensity

Discussion

Osmotic drug delivery is considered to be a delivery system which give constant drug release irrespective of agitation intensity. The drug release from optimised formulation was confirmed at various agitation speed i.e. 50, 100, and 150 RPM.

It is clearly evident from (table) that the release of BT from CPOP is independent of the agitation intensity. The $f1$ and $f2$ values were found to be $f1$ 4.05 and 79.47 (between 50 RPM and 100 RPM), $f1$ 2.44 and 88.38 (between 100 RPM and 150 RPM) for $f1$ 3.92 and $f2$ 76.75 (between 150 RPM and 50 RPM).

Hence, it can be expected that the release from the developed formulation will be independent of the agitation conditions of the absorption site.

4.6.3.4 Effect of dissolution volume

Optimised formulation was subjected to drug release at 50 RPM in combination of SGC for 2 hr followed by SIF in different dissolution volume. The resulted were plotted against time the figure 9-4 shows graph plotted and table 21-4 shows summarized results.

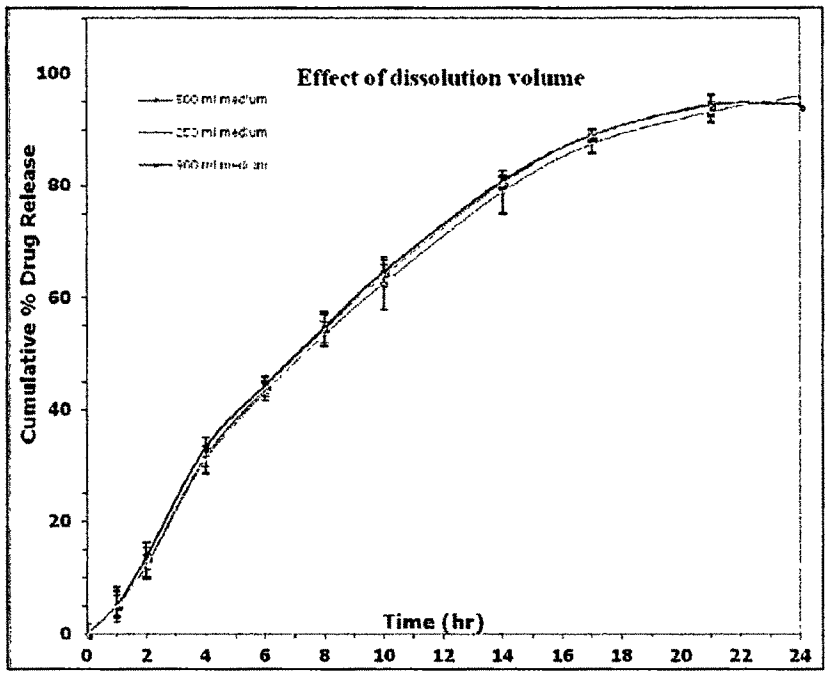


Figure 9 - 4 Drug release effect of dissolution volume.

Time (hr)	500 ml	SD	250 ml	SD	900 ml	SD
1	5.23	1.65	5.23	1.65	5.03	1.58
2	13.89	3.12	12.64	2.42	12.22	2.00
4	33.40	2.45	31.76	2.81	31.14	2.07
6	44.44	1.66	43.72	1.88	43.20	2.43
8	54.71	1.52	54.29	1.37	53.43	1.55
10	64.68	2.83	63.97	2.85	62.56	2.20
14	80.88	2.21	80.42	1.95	78.94	4.74
17	89.05	1.13	89.03	1.13	87.51	3.85
21	94.49	0.96	94.29	1.17	93.23	1.68
24	94.55	1.82	94.55	1.82	96.00	1.82

Table 21 - 4 Drug release data effect of dissolution volume

Discussion : Osmotic drug delivery is considered to be a delivery system which give constant drug release irrespective of volume if sink condition is maintained. The drug release from optimised formulation was confirmed at different release volume i.e. 250, 500, and 900 ml.

It is clearly evident from (table) that the release of BT from CPOP is independent of the dissolution volume. The $f1$ and $f2$ values were found to be $f1$ 0.94 and 95.10 (between 250 ml and 500 ml), $f1$ 2.60 and 86.27 (between 900 ml and 500 ml) and $f1$ 1.67 and $f2$ 91.78 (between 900 ml and 250 ml).

Hence, it can be expected that the release from the developed formulation will be independent of the volume at the absorption site.

4.6.3.4 Dose Dumping Study

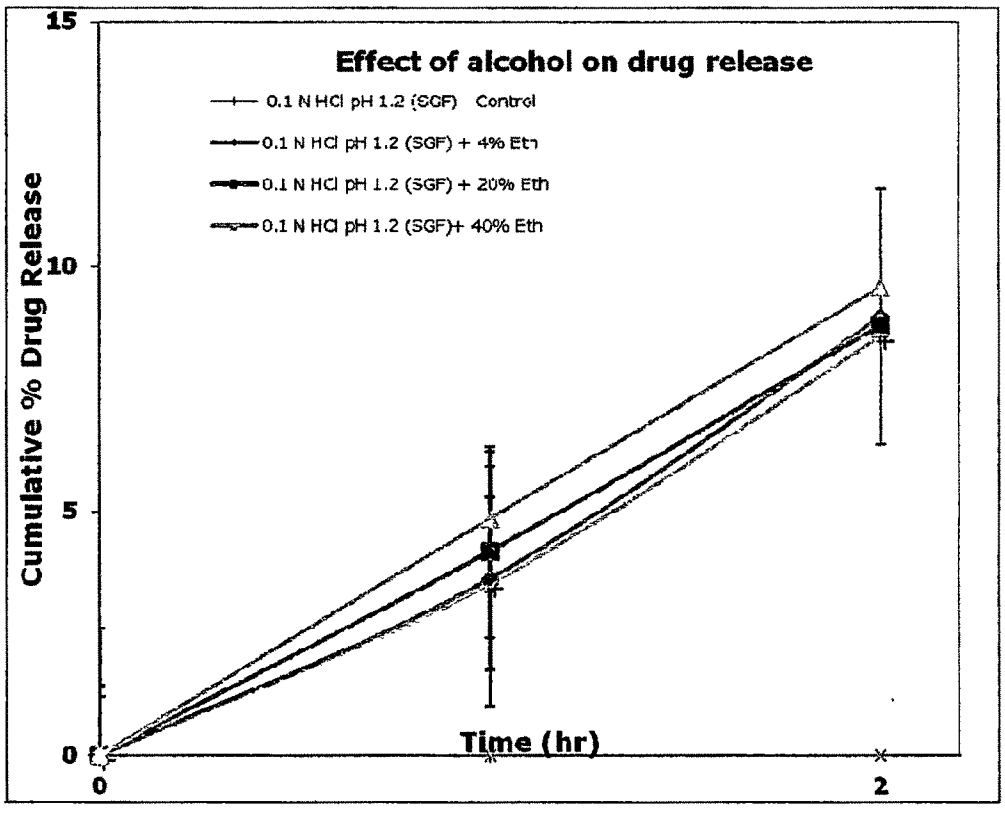


Figure 10 - 4 Dose dumping study

Discussion

In order to study the effect of alcohol on drug release or to verify weather alcohol leads to dose dumping 4 % V/V, 20 % V/V and 40 %V/V alcohol was added in the release media and drug release was verified against control (without alcohol).

Dose dumping is most commonly seen in drugs taken by mouth and digested in the gastrointestinal tract. Around the same time patients take their medication, they can also ingest other substances like fatty meals or alcohol that increase drug delivery. The substances may act on the drug product to speed up drug release, or they may stimulate the body's absorptive surfaces to increase the rate of drug uptake. Developed formulation was subjected to ethanol induced dose dumping study to emulate a "worst case" scenario. It was observed that no major

impact of alcohol on drug release. Hence, it is expected that accidental co-administration of alcohol will not lead to any dose dumping.

Curve fitting analysis

In order to describe the kinetics of drug release from controlled release preparations various mathematical equations have been proposed in the literature. Release data obtained was applied to different release models in order to establish the drug release mechanism and kinetics. Best goodness of fit test (R2) was taken as criteria for selecting the most appropriate model. The values are tabulated below.

Model	Zero Order	First Order	Higuchi Model	Peppas
Calculated R^2	0.9876	0.7400	0.9623	0.9834

Table 22 - 4 Calculated R2 Values for Developed formulation for differnt models

Discussion

Calculated R^2 for Zero order of drug release is nearest to 1, and osmotic pumps shows zero order of drug release. It can be concluded that the drug release from developed controlled porosity osmotic pump gives constant drug release.

4.6.3.5 Surface analysis of coating before dissolution and exhausted shell after dissolution use SEM

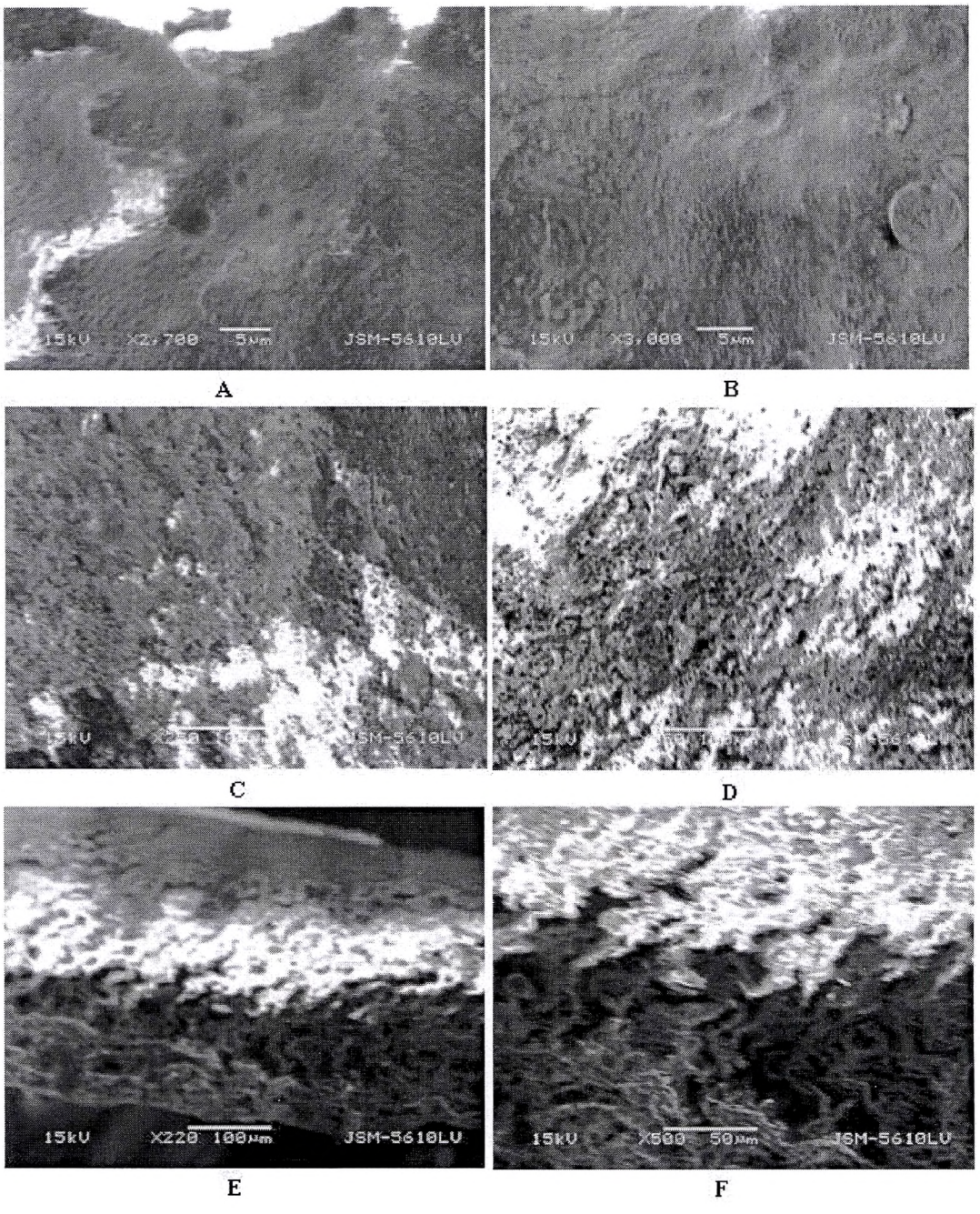


Figure 11 - 4 SEM images of Surface analysis of coating membrene before dissolution and exhausted shell after dissolution:

Surface of coated tablets before and after dissolution studies, was observed using scanning electron microscope (SEM). The morphology of the exhausted osmotic pump shell was analyzed using SEM (Surface Electron Microscopy).

Discussion : The drug release from the CPOP is anticipated due to formation of channels which forms on solubility of the pore former i.e Sorbitol in this membrane rendering the coating semi permeable allowing ingress of dissolution media followed by release of drug due to osmotic pressure. Formation of channels was confirmed by observing the coating membrane before and after the dissolution under surface electron microscopy. First two pictures Figure 11- 4 A (captured at 15kv X 2700) & Figure 11- 4 C (captured at 15kv X 250) shows no channel formation before dissolution. Second two pictures Figure 11- 4 B (captured at 15kv X 3000) & Figure 11- 4 D (captured at 15kv X 250) shows formation of pores in the coating membrane top view after dissolution. Third two pictures Figure 11- 4 E (captured at 15kv X 220) & Figure 11- 4 F (captured at 15kv X 500) shows pores are actually channels in the coating membrane side view of the coating membrane after dissolution.

Hence, it is confirmed that drug release in the developed formulation is through pores and channels formed due to pore former in the coating composition.

4.6.3.6 Observation of before and after dissolution

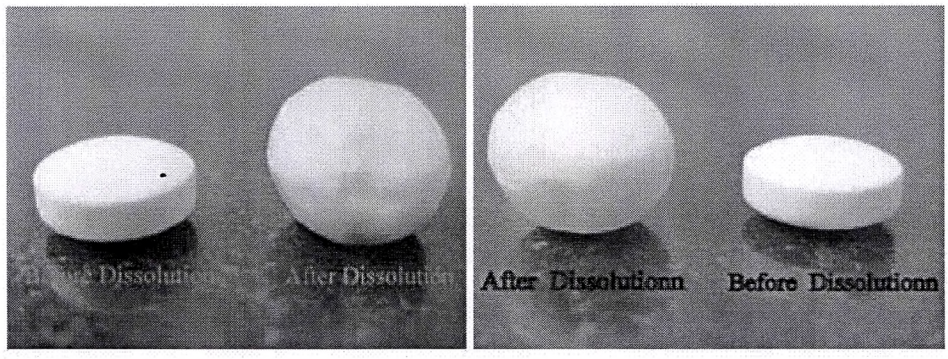


Figure 12 - 4 Physical observation of CPOP before and after dissoltion

Discussion : Physical change in the dimension of the tablet was observed. It was observed that it bulge after dissolution. Diameter of the tablet after & before dissolution was 12 mm and 9 mm respectively. The shape of enlarged table after dissolution changed to oval which was hollow filled with liquid inside and intact coating membrane see figure 12-4.

Hence, it was confirming the drug release through dissolution and movement through coating membrane in solution using osmotic pressure as driving force.

Drug release mechanism

To ensure the major mechanism of drug release, release studies of the optimized formulation were conducted in media containing saturated solution of osmotically active solute. Sodium chloride was added in dissolution medium. Saturated solution of sodium chloride produces osmotic pressure in the range of 356 atm. The pH of the medium was adjusted to 6.8 ± 0.05. Release studies were carried out in 250 ml of media using USP II dissolution test apparatus (50 rpm).

4.7 Result of Development studies

Optimised Dosages Form:

Butorphanol Tartrate Controlled porosity Osmotic pump is developed as white coloured, circular, biconvex, coated tablet dosage form for oral administration.

Formulation Details:

Controlled porosity Osmotic Pump is white colored, circular, biconvex coated tablet plain on both sides containing 10mg of Butorphanol Tartrate and following are inactive ingredients Sodium Chloride, Lactose Monohydrate, Microcrystalline Cellulose, Polyvinyl Pyrrolidone, Magnesium Stearate, Silicon Dioxide, PEG, D – Sorbitol etc and Isopropyl Alcohol, water and Acetone as solvent which shall not be part of final product.

Packing Profile:

Dosage form to be packed in HDPE Bottle pack of 100s.

4.7.1 Components of the Drug Product:

The quantitative composition (per tablet and % W/W), compandial status and function of each component used in the developed drug product is provided below in table 23-4.

Formula ingredients	Specification	Function(s)	Quantity (mg/tablet)	Quantity (% w/w)
Dry Mixing Stage :				
Butorphanol tartrate	USP	API	10.00	4.10
Sodium Chloride	USP NF	Osmogen	100.00	40.99
Lactose Monohydrate*	USP NF	Osmogen	100.00	40.99
PVP K 30	NF	Binder	12.00	4.92

Formula ingredients	Specification	Function(s)	Quantity (mg/tablet)	Quantity (% w/w)
Isopropyl Alcohol**	USP NF	Processing Solvent	Q.s.	Processing Solvent
Total weight of core tablet			**222.00**	**91.00**
Lubrication Stage :				
Mg. Stearate	USP NF	Glidant	3.00	1.23
Talc/Purified Talc	USP NF	Antiadherent	3.00	1.23
Colloidal silicon dioxide	USP NF	Lubricant	2.00	0.82
Total weight of core tablet			**230.00**	**94.00**
Coating Solution : For 6 % Weight Gain (Calculated values)				
Cellulose CA398-10	USP NF	Film Forming Agent	7.34	2.86
PEG 400	Ph.Eur	Plasticizer	5.43	2.11
D – Sorbirol	IP	Pore Forming Agent	1.91	0.74
Purifies Water **	IH	Processing Solvent	Q.s.	Processing Solvent
Acetone**	IP	Processing Solvent	Q.s.	Processing Solvent
Total weight of coated tablet after coating			**245**	**100.00 %**

Table 23 - 4 Optimised compostion after development studies

* Quantity is compensated depending on the potency of Butorphanol tartarte to maintain tablet weight constant.** Used as processing solvent, does not remain in the final product.

4.7.2 Optimised Coating Solution composition

Ratio of solids used in coating solution is Critical Process parameter and it has direct impact on drug release optimsed coating formulation is summarized in table 24-4.

Ratio of solids used in coating solution	
Cellulose Acetate	50 % w/w
D -Sorbitol	37 % w/w
PEG - 400	13 % w/w
Ratio (Acetone : Water : Solid)	
Acetone	86.00 % w/w
Water	10.00 % w/w
Solid	4.00 % w/w

Table 24 - 4 Optimised coating compostion - development studies

4.7.3 Critical Quality Attributes: (CQAs)

1. Blend Uniformity
2. Uniformity of weight
3. Assay
4. Dissolution
5. Uniformity of Dosage unit
6. Stability

4.7.4 Critical Process Parameters (CPPs)

1. Blending process (Time, Speed, Agitation intensity, Room Temperature (Humidity).
2. Dry Mixing time (Geometric Mixing and Sieve size)
3. Compression (Speed, Compression force)
4. Coating (Pan RPM, Broader spray pattern, Inlet and outlet air CFM, Inlet and outlet air temperature)

4.8 Conclusion:

Stable 10 mg of butorphanol tartrate extended release COPO formulation is developed which gives drug release independent of agitation intensity, pH and dissolution volume, rendering the drug release through osmotic pressure at constant and is expected to provide desired in-vivo performance.

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